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ANTICOAGULANT THERAPY OF OCCLUSION OF CENTRAL VEIN OF RETINA

IN RELATION TO PATHOGENESIS AND DIFFERENTIAL DIAGNOSIS

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The increasing number of reports during the past two years [1] of the results of heparin therapy in retinal venous occlusion should focus interest again on the various mechanisms by which this condition is produced, of which there are four. As will be shown, these four different types of pathologic change are by no means equally amenable to this anticoagulant therapy. In the present paper, special emphasis is placed on the differential diagnostic points which determine the pathogenesis of the occlusion and hence the success of therapy with heparin and dicoumarin (3,3′-methylene-bis[4-hydroxycoumarin]).

The pathogenesis of the first and perhaps the most frequent type of occlusion of the central retinal vein, that on the basis of systemic angiosclerosis in older persons, has been elucidated by the investigations of Harms,[2] Scheerer,[3] Verhoeff [4] and Hertel.[5] In the course of an essentially chronic sclerotic atrophic process, which affects the central vessels, the central connective strand and the lamina cribrosa, the lumen of the vein is gradually narrowed by compression from outside the vessel. The central artery is transformed into a rigid tube by thickening

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1. Holmin, N., and Ploman, K. G.: Thrombosis of Central Vein of Retina Treated with Heparin, Lancet **1**:664, 1938. Ploman, K. G.: Heparin Treatment of Thrombosis in Central Vein of Retina, Acta ophth. **16**:502, 1938. Rea, R. L.: Treatment of Thrombosis in Central Vein of Retina with Heparin, Arch. Ophth. **25**:548 (April) 1941. Rychener, R. O.: Heparin and Thrombosis, Memphis M. J. **16**:61, 1941. McDonald, A. E.: Heparin in Thrombosis of the Central Vein, Tr. Am. Ophth. Soc. **38**:313, 1940.

2. Harms, C.: Anatomische Untersuchungen der Gefässerkrankungen im Gebiete der Arteria und Vena centralis retinæ, Arch. f. Ophth. **61**:1, 1905.

3. Scheerer, R.: Zur pathologischen Anatomie der Netzhaut-Zentralgefässe, Arch. f. Ophth. **112**:218, 1923.

4. Verhoeff, F. H.: Obstruction of the Central Retinal Vein, Arch. Ophth. **36**:1, 1907.

5. Hertel, O.: Beitrag zur Angiosclerose der Zentralgefässe des Auges, Arch. f. Ophth. **52**:191, 1901.

of its adventitia, which at the same time loses much of its elastic fiber content. The intralaminar central connective tissue strand is thickened as a whole, and between artery and vein, where under normal conditions no scaffolding of connective tissue is present, fibrous bands and cuneiform masses of fibrous tissue form, separating the venous and the arterial lumen more and more and tending to compress still further the walls of the already only semilunar venous aperture. A well developed glial meniscus (Salzmann [6]) within the anterior part of the lamina cribrosa may encroach on the patency of the vein in this region still more. Whenever the compression of the vein has reached a stage of complete closure of the lumen at one or more places, an irritative proliferation of the endothelium and often of the subendothelial layers sets in, which accelerates the venous occlusion. In the following case, this type of histopathologic change was found in the study of the enucleated right eye:

CASE 1.—N. N., a man aged 64, had noted sudden and painless failure of vision of the right eye five months prior to his first visit to the clinic. The right eye was totally blind, was intensely injected and had an incipient serpent ulcer. The iris was extremely hyperemic, and the tension was increased to 51.5 mm. Schiøtz. The left eye was normal. The systemic blood pressure was 104 systolic and 82 diastolic.

The histopathologic changes in the enucleated right eye were those of an old occlusion of the central retinal vein with secondary glaucoma. A cross section through the optic nerve within the anterior half of the lamina cribrosa, stained by Verhoeff's elastica method, is shown in figure 1.

The stage of slitlike narrowing of the venous lumen within the lamina cribrosa there illustrated predisposes to secondary thrombus formation. Although attempts to counteract this event with anticoagulant therapy may be made, one should keep in mind that the thrombus formation may be only the last short step to complete occlusion of an already narrow lumen. Hence any improvement resulting from this therapy may be of short duration and may be only a postponement of the inevitable occlusion by the primary sclerotic process.

The not infrequent, often bilateral, occlusion of the central vein in generalized carcinomatosis may be explained by a similar mechanism, i. e., compression of the vein from outside the vessel by rapidly growing tumor metastases into the optic nerve near the central vessels, illustrated by figure 2. Both local and general conditions would tend to make anticoagulant therapy futile for such occlusion.

A second type of occlusion of the central retinal vein, with an entirely different pathogenesis, is that occurring in such blood dyscrasias as polycythemia vera and primary thrombocythemia. The predisposition to thrombosis in some patients with polycythemia vera is well known

6. Salzmann, M.: Glaukom und Netzhautzirkulation, Abhandlungen aus der Augenheilkunde und ihren Grenzgebieten, Berlin, S. Karger, 1933, no. 15.

and is not limited to one special vascular field. Jürgens [7] demonstrated that by careful hematologic study patients with polycythemia vera who showed an inclination to thrombus formation could be easily separated from the group without such a tendency. Patients who later showed symptoms of thrombotic vascular occlusions in various organs had always a reduced coagulation time, a high globulin content in the plasma and, most important of all, an increased number of thrombocytes

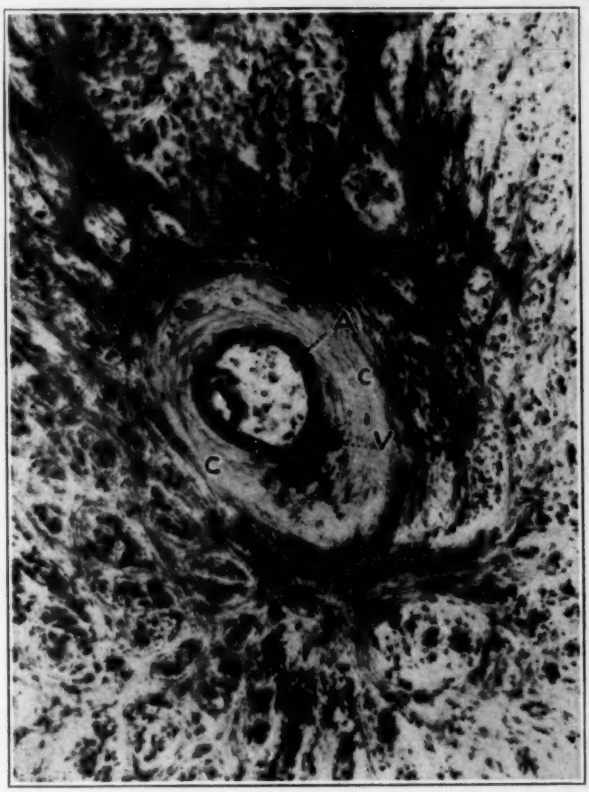

Fig. 1 (case 1).—Cross section through the optic nerve within the anterior half of the lamina cribrosa (Verhoeff's elastica method). *A*, sclerotic central artery, i. e., elastica interna markedly thickened, lumen partially filled with endothelial and subendothelial proliferation and adventitia poor in elastic fibers. *V*, central vein restricted to a semilunar space, lumen completely obliterated and endothelial proliferation especially pronounced at the compressed slitlike edges. *C*, thickened central connective tissue strand, poor in elastic fibers.

(platelets). Patients with polycythemia in whom the tendency to thrombosis was absent were normal in these respects. Jürgens stated

7. Jürgens, R., and Bach, K.: Thrombosebereitschaft bei Polycythaemia vera, Deutsches Arch. f. klin. Med. **176**:626, 1934.

the belief that the increased number of thrombocytes is the deciding factor.

Primary thrombocythemia has received much less attention in the literature than polycythemia vera, but in some reports of patients with this condition (Rowlands and Vaizey [8]), multiple thrombus formation in the mesenteric, pulmonary and peripheral vascular systems dominated the picture.

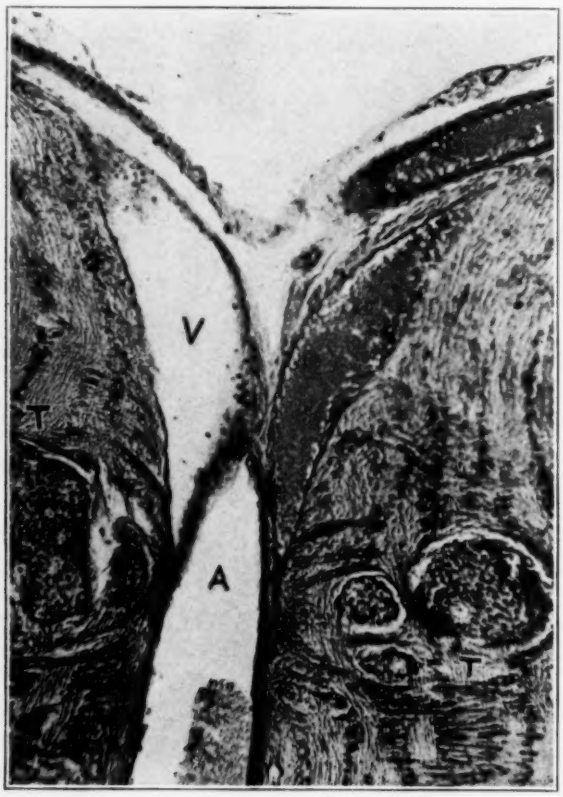

Fig. 2.—*A* and *V*, central artery and vein surrounded by tumor metastases into the optic nerve of the left eye of a woman aged 58 with carcinoma of the mammary gland. *T*, tumor metastasis into the optic nerve within the anterior portion of the lamina cribrosa.

Of interest in this connection are the statistics reported from the Cleveland Clinic by Zeiter,[9] who found vascular disease in 20 per cent of 31 patients with polycythemia vera. There were 6 patients in whom the lesions were in the cerebral, coronary, mesenteric or peripheral

8. Rowlands, R. A., and Vaizey, J. M.: Primary Thrombocythaemia, Lancet **2**:1217, 1938.

9. Zeiter, W. J.: Peripheral Vascular Disturbances in Polycythaemia, M. Clin. North America **24**:435, 1940.

vessels, the last being predominantly affected. Four of these patients were between 62 and 75 years of age, and 3 of the 4 had definite hypertension. This author did not mention thrombocythemia.

The importance of a coexisting vascular disease in patients with these blood dyscrasias should not be underestimated in considering the pathogenesis of thrombosis, including that within the central retinal vein. A combination of the predisposing factors of increased blood volume, high viscosity, slowing of the blood flow, easy coagulability of the blood with otherwise negligible alterations in the venous wall or a slight narrowing of the venous lumen, together perhaps with preexisting unfavorable anatomic relations, may give rise to primary thrombus formation.

Such patients whenever they show the fundus picture of a partial or complete retinal venous occlusion should benefit from any therapy directed against their general tendency to thrombus formation, provided not too much time has elapsed since the vascular accident. Heparin and dicoumarin have to be considered for immediate and rapid action, perhaps to be supported later by roentgen irradiation of the bone marrow, this therapy being directed mainly against the hyperfunction of the megakaryothrombopoietic system, which is more sensitive to this irradiation than the erythropoietic system (Jürgens [7]).

This type of pathogenesis (type II occlusion) is well illustrated in the following case, in which the patient was first seen during a mild but prolonged attack of incipient occlusion of the central vein of the retina of the left eye:

CASE 2.—Mr. C. G., 64 years of age, first entered the outpatient eye clinic at Rush Medical College on Jan. 27, 1941, after five weeks of intermittent blurring of vision of the left eye, vertigo and a sensation of fulness in the left side of the head. The duration of each of these attacks was from several hours to an entire day. At no time was the right eye affected in a similar manner. Two additional attacks of occlusion of the central vein, each of great severity, occurred in the left eye during the next year and a half. Heparin therapy was employed in the first two attacks and dicoumarin in the third.

During the first attack, there was a narrow arcuate scotoma extending from the lower pole of the (left) blindspot to within 2 degrees of the fixation point, but there was no reduction of the central vision. Ophthalmoscopic examination revealed a mild retinal angiosclerosis of both eyes; the veins were rather tortuous and darker than normal. In the left eye, there was edema of the temporal and superior margins of the disk and of the contiguous portion of the retina, extending over the entire superior portion of the macular area. The retinal veins were enormously dilated, tortuous and dark. Throughout the distribution of the retinal venous vascular tree there were numerous perivascular round and flame-shaped retinal hemorrhages, some having yellowish centers. The inferior retinal vein emerged from the papilla as a single broad trunk (congenital anomaly), instead of the usual temporal and nasal branches, dividing into these branches only at a point about 3 disk diameters below the disk.

The results of general physical examination were not of great significance, but there was a definite reddish, congested appearance of the skin, especially of the

face. The systemic blood pressure was 142 systolic and 98 diastolic; the liver and spleen were not palpably enlarged.

Examination of the blood revealed findings of the greatest importance, as follows: erythrocytes 5,080,000, leukocytes 7,350, thrombocytes 1,417,320 and hemoglobin content 86 per cent. The serum content of calcium was 9.8, of phosphorus 3.0 and of cholesterol 332 mg. per hundred cubic centimeters. The coagulation time was thirty seconds (normal five minutes), and the bleeding time was normal. There was marked anisocytosis of the thrombocytes, about half of them being larger than normal.

The patient remained under observation during four months without heparin therapy, because of lack of funds to pay for the material. During this time there was a slow improvement in the clinical picture, with some lessening of the retinal edema and venous congestion. At the end of this time, however, visual obscurations became more frequent and prolonged and the retinal veins more congested. The patient was admitted to the hospital on May 23; heparin therapy was begun on that day and continued for a six day period. The total amount of heparin employed was 1,549 mg. During the first two days, the method of continuous venoclysis was used, and for the remaining four days, intermittent intravenous injection.

On the second day of this therapy some new retinal hemorrhages of small size were noted along the inferior temporal vein and the terminal branches of the superior temporal vein. No further hemorrhage occurred, and on termination of this course of therapy after six days, the edema of the optic nerve and retina had disappeared, and the color and caliber of the retinal veins had returned to approximately normal. Of the greatest significance were the changes in the blood. The coagulation time, determined every four hours during this period, was markedly increased, varying from five to twenty-three minutes. The thrombocyte count had dropped one week after therapy from over 1,400,000 to 351,000 and later to 260,000. This reduction has remained to the present time. The prothrombin level was 142.3 per cent. The arcuate scotoma was reduced to two small insular remnants; subjective symptoms of visual obscuration, vertigo and headache disappeared.

For two months after this course of heparin therapy, there were no signs or symptoms of recurrence. Then the second attack was ushered in by occasional brief attacks of dimness of vision of the left eye, becoming more severe and prolonged, until the visual acuity of the left eye was reduced on August 8 to 4/200 and on August 10 to 2/200. The fundus picture of occlusion of the central vein was again present, but in more severe form, with enormous venous engorgement, more pronounced edema of the papilla and retina and large retinal hemorrhages. The coagulation time was reduced to a few seconds, but the thrombocyte count was only 325,000 (i. e. normal). The patient was again hospitalized, and the second course of heparin therapy was begun within seventy-two hours of the complete occlusion of the central vein and continued for eight days, 2,100 mg. of heparin being used. On the third day, many fresh punctate capillary retinal hemorrhages appeared along the terminal venous branches. On the fifth day, the visual acuity recovered to normal (1.2). After ten days, the retinal edema subsided, and the thrombocyte count fell to 171,600; the prothrombin level was 146.6 per cent. The coagulation time increased greatly during therapy, varying from four to more than sixty minutes. Nothing abnormal was revealed by sternal puncture.

For five months there were no subjective symptoms, and with gradual absorption of the retinal hemorrhages, the fundus of the left eye regained an almost normal appearance.

At the end of this period an attack occurred of severe generalized headache and temporary dimness of vision of the left eye. There were again some edema of the retina and a few small hemorrhages along the superior and inferior temporal veins, which appeared congested. For the first time, in the upper half of the disk

two venous loops were noted projecting from the surface of the optic papilla close to the venous side of the central vascular funnel. They were interpreted as venous anastomoses which had developed gradually during the past five months.

Anticoagulant therapy was employed again to prevent the apparently imminent venous occlusion, dicoumarin being used this time instead of heparin. The patient entered the hospital on Jan. 20, 1942, at which time there were 260,000 thrombocytes and continued anisocytosis. Examination of the blood showed the value to be 10.8 mg. per hundred cubic centimeters for serum calcium, 3.8 per cent for albumin, 2.5 per cent for globulin and 0.41 per cent for fibrinogen. The erythrocytes numbered 4,550,000 and the leukocytes 6,600, and the hemoglobin content was 85 per cent. The bleeding time was two and one-half minutes, the coagulation time twelve seconds, the prothrombin level 155 per cent (two stage method) and the blood pressure 155 systolic and 85 diastolic.

One hundred milligrams of dicoumarin daily was given orally in split doses for five days. The prothrombin level was reduced to 100 per cent on the fifth day and gradually rose to its former level during the following two weeks. The coagulation time rose temporarily to three minutes on the fourth and fifth days and returned to fifty-five seconds within three days after that. The retinal edema disappeared during this time, the congestion of the veins lessened and the two formerly engorged anastomotic loops receded into the nerve tissue and were barely visible.

As the venous congestion did not disappear completely and intermittent visual obscurations persisted, a second course of dicoumarin therapy was begun on February 27, and 200 mg. of dicoumarin daily was given orally for five days. While the coagulation time rose only to four minutes and varied, beginning with the second day, between only one and four minutes during the following eight days, the prothrombin level fell to 75 per cent on the third day, 48 per cent on the fifth day and 46.5 per cent on the seventh and from then on gradually rose again, being 75 per cent on the twelfth day, 120 per cent on the seventeenth day, 130 per cent on the twenty-fifth day and 142 per cent six weeks later. At no time during the two dicoumarin series did fresh retinal hemorrhages appear, as during therapy with heparin.

After the second course of dicoumarin therapy, the caliber of the retinal veins returned to normal, and the venous loops in the upper half of the papilla receded completely into the optic nerve. The left eye recovered vision of 1.5, which has been retained to the present time. Headaches, vertigo and visual obscurations ceased completely. A physical examination and tests of the liver function revealed no untoward effect of the dicoumarin therapy.

The interpretation of the general status of this patient is difficult. The two predominant features are the abnormal hematologic findings, on the one hand, and a mild senile arteriosclerotic hypertension, on the other. The tremendous increase of thrombocytes over a long period without any other organic or constitutional pathologic changes and the persistence of the high prothrombin level and of the morphologic abnormalities of the platelets suggest the category of mild primary thrombocythemias. Perhaps a mild senile arteriosclerotic process predominantly localized in the spleen could produce this clinical picture (Epstein and Goedel[10]). The anisocytosis of the platelets persisted

10. Epstein, E., and Goedel, A.: Hämorrhagische Thrombocythämie bei vasculärer Schrumpfmilz, Virchows Arch. f. path. Anat. **292**:233, 1934.

throughout the therapeutic measures, indicating a continuous qualitative insufficiency, perhaps due to an unusually rapid formation. The permanent reduction of the number of platelets by heparin cannot be explained, since nothing is yet known concerning the mechanism of the action of heparin or of dicoumarin. It would seem that in those cases in which there are at the same time an increased number of platelets and a high prothrombin level, it might be more satisfactory to use the two drugs at the same time.

The ocular events in the left eye of this patient must be interpreted as a slowly increasing venous circulatory disturbance, which at various times during the period of observation culminated in an almost complete occlusion of the central vein through a combination of hematopathologic conditions favoring thrombus formation, and a certain degree of vascular sclerosis. Recovery from the attacks through the effect of anticoagulants gave the necessary time for the development of anastomotic channels.

It is probable that the patient will have more attacks of partial or even complete occlusion of the central vein, but it is hoped that reestablishment of a venous lumen with the aid of anticoagulants, even if it becomes increasingly narrow owing to the undoubtedly increasing vascular sclerosis, will give sufficient time for the development of an effective collateral venous circulation, the beginnings of which have already been noted in the two venous loops, which dilated markedly at the time when the lumen of the central vein became obstructed.

The third type of occlusion of the central retinal vein may be designated as stagnation thrombosis. The mechanism has been fully recognized only recently, by Seidel,[11] although Theodor Leber had already suggested the possibility. Seidel examined a woman, 45 years of age, who had a pronounced vasoneurotic constitution, a few minutes after she had noted a visual obscuration in one eye. He found a pronounced generalized contraction of the retinal arteries, which was followed after about thirty minutes by retinal edema, especially severe around the macula, which presented the characteristic cherry red spot. After ten days, extensive retinal hemorrhages had occurred, and the ophthalmoscopic picture of occlusion of the central artery was transformed into that of occlusion of the central vein.

The first requisite for stagnation thrombosis is the production of a sudden decrease of the arterial retinal blood supply by a widespread arterial spasm. This sudden diminution of the retinal arterial blood volume leads to a slowing of the venous circulation and may reduce the pressure within the central vein to a point so much lower than the intraocular pressure that the vein collapses at the point where its pressure is lowest.

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11. Seidel, E.: Zur Entstehung des Krankheitsbildes der Thrombose der Vena centralis retinae, Arch. f. Ophth. **141**:151, 1939.

A coexisting mild degree of vascular sclerosis, such as was present in the eye of Seidel's patient, which was also histologically studied, would add to the probability of thrombus formation mainly at and peripheral to the place of lowest pressure in the central vein.

In the third type may be included the following etiologic situations: (*a*) early hypertension with marked spastic episodes, before extensive organic arteriolar lesions develop; (*b*) a general surgical procedure or cranial fracture (Gürsel,[12] Zoldan [13]), and (*c*) congenital heart disease with compensatory polycythemia, in which constant irritation of the bulbar vasomotor centers and of the vessel walls themselves by the carbon dioxide–rich blood has led to extensive arterial constriction (Baquis [14]).

Heparin or dicoumarin therapy should be of definite value for this type of occlusion, with the support of vasodilators to counteract the venous stasis.

The fourth type of retinal venous occlusion is that caused by inflammatory disease of the venous wall, which leads to complete occlusion of the venous lumen by secondary thrombus formation. The most frequent example is tuberculous retinal periphlebitis. The alterations of the venous walls in this condition may consist either of nonspecific proliferative inflammatory changes on an allergic basis, beginning with a round cell infiltration in the perivascular lymph spaces, which gradually encroaches on and destroys the venous walls (Axenfeld [15]), or, in rarer instances, of real tuberculous granulation tissue, which may project as a nodule into the venous lumen (Verhoeff,[16] Friedenwald,[17] Šafář [18]). In either event the end result is an extreme narrowing of the venous lumen at a place where the venous walls are maximally diseased, and the secondary thrombus formation in such places, whether in the central vein or in one of its branches, serves to diminish rather than to increase

12. Gürsel, A. E.: Prostatectomy Followed by Thrombosis of Central Retinal Vein, Türk tib cem. mec. **6**:280, 1940.

13. Zoldan, L.: Considerazioni infortunistiche sopra un caso di trombose traumatica della vena centrale della retina, Rassegna d. previd. sociale **25**:55, 1937.

14. Baquis, E.: Ueber pathologische Anatomie und Pathogenese der Cyanosis retinae, nebst Bemerkungen über die Pathogenese des Glaukoms, Arch. f. Ophth. **68**:177, 1908.

15. Axenfeld, T., and Stock, W.: Ueber die Bedeutung der Tuberkulose in der Aetiologie der intraokularen Hämorrhagien und der proliferierenden Veränderungen in der Netzhaut, besonders über Periphlebitis retinalis bei Tuberkulösen, Klin. Monatsbl. f. Augenh. **49**:28, 1911.

16. Verhoeff, F. H., and Simpson, G. V.: Tubercle Within Central Retinal Vein: Hemorrhagic Glaucoma: Periphlebitis Retinalis in Other Eye, Arch. Ophth. **24**:645 (Oct.) 1940.

17. Friedenwald, J. S., in discussion on Verhoeff and Simpson,[16] p. 652.

18. Šafář, K.: Ueber Drucksteigerung im Gefolge der juvenilen Netzhaut Glaskörperblutungen und Verschluss der Zentralvene infolge tuberkulöser Phlebitis, nebst Bemerkungen über die Entstehungsweise der Netzhautgefässtuberkulose, Arch. f. Ophth. **119**:624, 1928.

the hemorrhagic extravasations. Anticoagulants, therefore, are contraindicated.

This type of venous occlusion with underlying tuberculous phlebitic lesions of the second type was found in the following case:

CASE 3.—Mr. S. R.,[19] 34 years of age, was first examined twenty-four hours after the onset of pain in the left eye. Three months prior to this time, impairment of vision of this eye was first noted.

The clinical examination of the eyes revealed the visual acuity of the right eye to be normal, while that of the left was reduced to 6/200. The right eye was objectively normal except for a heavily pigmented choroidal lesion about 3 disk diameters above the disk and a vascular convolution on the disk. The retinal veins

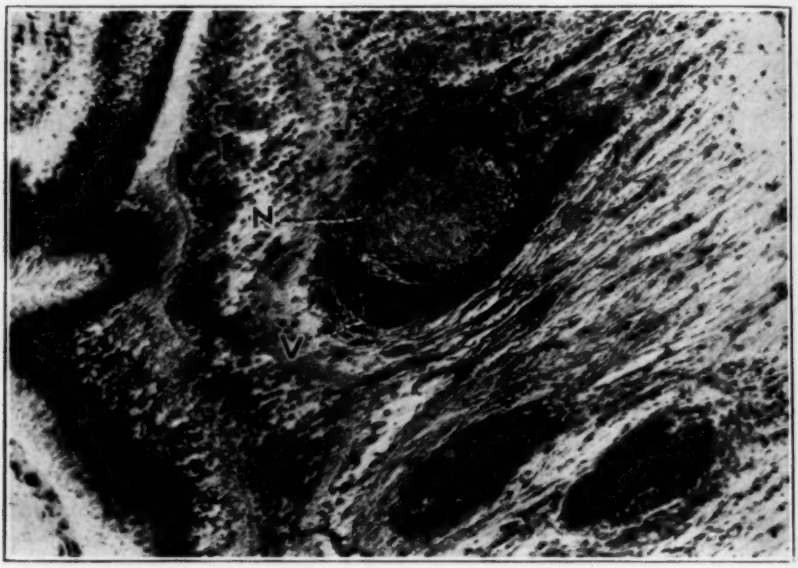

Fig. 3 (case 3).—Occlusion due to inflammatory disease of the venous wall (tuberculous periphlebitis). *V*, retinal vein. *N*, nodular thickening of the wall of the vein composed of epithelioid cells, round cells and giant cells. Partial thrombosis of the venous lumen along the diseased wall would tend to decrease rather than to increase hemorrhagic extravasations.

adjacent to the choroidal lesion were partly obliterated, and there were in this area a few small retinal hemorrhages. There was severe hemorrhagic secondary glaucoma of the left eye, which on histologic examination was found to be due to occlusion of the central vein by tuberculous periphlebitis. The intraocular tension was 50 mm. Schiøtz, and there was intense hyperemia of the anterior cilioepiscleral vessels and of the iris. There were extensive retinal hemorrhages throughout the posterior polar region, on the disk and extending into the periphery of the fundus. Between the hemorrhages were yellowish masses, and there were spindle-shaped aneurysms of some of the retinal veins.

Some of the details of the histologic picture are shown in figure 3.

19. Dr. Max Herzog supplied the clinical data on this patient, who is still under his care.

Thus it is of prime importance to the success of anticoagulant therapy in venous occlusion to make the most accurate clinical diagnosis of the type of occlusion. The following procedures should yield differential diagnostic points of value:

1. A search for angioneurotic tendencies in the family as well as in the personal history, with special reference to hypertension, migraine, coldness of the hands and feet and other indications of vascular disease.

2. A thorough examination of the vascular system, especially in older patients. As was stated in an earlier part of this discussion, vascular sclerosis, even if mild, plays a deciding role in the pathogenesis of all but the fourth type of venous occlusion.

3. A hematologic study with special attention to the number and shape of the platelets and of the megakaryocytes obtained by sternal punctures if indicated; determination of the calcium, globulin, fibrinogen and prothrombin levels, these being usually higher in patients with thrombotic tendencies.

4. Most important of all, a study of both fundi with regard to arterial spasm and visible signs of arteriosclerosis or phlebosclerosis, its degree and type (i. e., of the predominance of endovascular or perivascular processes). The presence or absence of physiologic venous pulsation should be noted as an indicator of the existing relationship of the venous and the intraocular pressure. It is known that pulsation of the central retinal vein depends on the ratio of the intraocular to the intracranial pressure and not on their absolute height (Serr [20]). Venous pulsation is absent if the intracranial and the venous pressure are higher than the intraocular pressure. So-called physiologic venous pulsation is therefore an indication of a condition which makes an eye more vulnerable for the development of stagnation thrombosis.

Another important factor which governs the success of heparin and of dicoumarin therapy is its early application, particularly in cases of occlusion of type I. As the action of these preparations is limited to the reduction of the coagulability of the blood and thus counteracts only thrombus formation, in such cases, in which the thrombus formation is secondary to severe sclerotic processes and is only the final step to complete occlusion of the already narrowed lumen, the time element is least favorable. Whatever moderate success might be expected has to be obtained quickly, perhaps within twenty-four or forty-eight hours after complete occlusion.

If, on the other hand, a primary thrombus forms in a vessel of normal caliber with only slight sclerotic changes in the wall or perhaps with only an abnormally tortuous, unfavorable course, a longer time for therapeutic possibilities after the occlusion can be expected. If the

20. Serr, H.: Zur Analyse der spontanen Pulserscheinungen in den Netzhautgefässen, Arch. f. Ophth. **137**:487, 1937.

occlusion by primary thrombosis is complete, two weeks or slightly longer may be suggested as the time limit beyond which anticoagulants would prove to have little or no effect, as by this time endothelial and subendothelial proliferation for organization of the thrombus is well under way. If the occlusion is only partial or incipient, favorable conditions for anticoagulant therapy may exist for a long time, as was demonstrated in case 2.

SUMMARY AND CONCLUSIONS

The mechanisms of occlusion of the central retinal vein are discussed and illustrated, and occlusion is classified into four types, as follows:

I. Occlusion by compression from without the vessel and secondary thrombus formation, as in some types of arteriosclerosis and phlebosclerosis or in tumor metastasis into the optic nerve. In these conditions anticoagulant therapy is of little or no value, as thrombus formation is only the terminal event bringing about complete occlusion of an already narrow venous aperture.

II. Occlusion by primary thrombus formation in blood dyscrasias, such as polycythemia and thrombocythemia. Heparin or dicoumarin therapy is of definite value, as illustrated by the report on a patient with incipient occlusion of the central vein in one eye who was thrice treated successfully with anticoagulants, the vision of this eye recovering from 2/200 to the present 1.5. The rapid action of these preparations may be prolonged and supported later, if necessary, by roentgen irradiation of the bone marrow.

III. Occlusion by stagnation thrombosis following widespread arterial spasms. To this type belongs venous occlusion caused by (*a*) early spastic hypertension, (*b*) a surgical procedure or cranial fracture and (*c*) congenital heart disease. Anticoagulants, perhaps supported by vasodilators, should be of definite value in the treatment of this type.

IV. Occlusion by inflammatory disease of the venous wall and secondary thrombus formation. The employment of anticoagulants is contraindicated.

The anticoagulants heparin and dicoumarin (3,3′-methylene-bis[4-hydroxycoumarin]) are valuable additions to the therapeutic armamentarium for the care of eyes with venous occlusion, whose vision otherwise might be lost, but the most accurate clinical classification of the type of occlusion should precede the employment of this therapy.

Dr. Evans W. Pernokis and Dr. Heyworth N. Sanford and their associates assisted with the hematologic problems in case 2. Dr. M. D. Hursch and Dr. Y. A. Staton, former residents at Presbyterian Hospital, assisted with the technical details of therapy and with the hematologic tests.

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IONTOPHORETIC INTRODUCTION OF ATROPINE AND SCOPOLAMINE INTO THE RABBIT EYE

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Repeated attempts were made to introduce the common mydriatics employed in ophthalmology by means of a galvanic current [1] because an increased activity of these drugs is desirable in a number of pathologic conditions of the eye. Rochat [1a] studied the iontophoretic administration of atropine and other alkaloids in experiments on rabbits and by clinical observation. When other clinical methods had failed, he demonstrated the effectiveness of the iontophoretic method in breaking resistant posterior synechias despite the low concentration of the atropine sulfate solution (0.1 per cent). Rochat based his conclusions on measurements of the pupils of treated eyes. He did not consider, however, the effect of electric current per se, which increases or decreases the size of the pupil in different degrees according to the strength of the current and the length and method of application. Quantitative determinations of the mydriatics found in different parts of the eye after iontophoretic treatment were therefore indicated. The experiments of the following series were carried out with atropine sulfate and scopolamine hydrobromide.

TECHNIC

For the iontophoretic introduction a corneal bath with a Birkhäuser electrode and a 45 volt dry cell battery were used. The cathode was held on the shaven back of the rabbit's head. The intensity of the current, length of the application and concentration of the solution were varied in the different series. In all experiments, the solution to be introduced was at room temperature. The results of experiments with iontophoresis were compared with those of control experiments consisting of a bath without the current and subconjunctival injection. The concentration in the aqueous following repeated instillations of 1 per cent atropine sulfate solution were unreadably low. Besides the corneal route, two transcleral routes were tested: first, through the conjunctiva and sclera in a ring-shaped zone

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1. (*a*) Rochat, G. F.: L'iontophorèse des mydriatiques dans le traitement des irites et des iridocyclites, Internat. Ophth. Cong., Amsterdam **1**:196, 1929. (*b*) Polner, S.: Ukrain. oftal. zyzn., 1930, vol. 1; cited by Karbowski.[8] (*c*) Jusefova, F., and Kroll, A.: Zur Frage der Atropiniontophorese in der Augenpraxis, Arch. oftal. **8**:296, 1931; abstracted, Zentralbl. f. d. ges. Ophth. **26**:790, 1932.

(equal in area to the cornea) between the limbus and the ora serrata and, second, through the freely exposed sclera in the region of the equator of the eye. A special applicator was made [2] for the iontophoresis toward the ciliary body and the iris, consisting of two tubes, of which the inner fitted the limbus and the outer rested 5 mm. beyond, approximating the position of the ora serrata. A spiral wire, contained in a widening of the outer tube similar to Van Heuven's [3] electrode, was connected to the anode. The space between the two tubes was filled with the solution of the salt to be introduced. For the application at the region of the equator, the conjunctiva was incised in the upper half, the superior rectus and superior oblique muscles were resected or displaced by a suture to expose the sclera and a Birkhäuser electrode 10 mm. in diameter was placed *in situ*. The eyes were removed one hour after treatment and the alkaloid content of the aqueous, the vitreous and, in some series, the iris with ciliary body determined.

The amount of alkaloid which penetrated into the eye with dilute solutions and a weak current was too small for quantitative chemical determination. Bioassay was therefore used and the pupil of the white mouse selected as the most sensitive test object according to the method of Pulewka.[4] The superiority of the estimation of compounds of the atropine group by means of the pupil of the white mouse over the better known method involving the pupil of the cat was confirmed by Veit and Vogt [5] and Orzechowski and Hundrieser.[6] The instillation of 1 drop of 0.01 cc. containing 0.000006 mg. of atropine sulfate will double the size of the pupil, but the salt concentration and the p_H of the solution to be tested may alter the effect. Therefore the less sensitive subcutaneous or intraperitoneal injection was preferred. It gave reliable results when the test injection exceeded 0.0005 mg. The quantity of the solvent was varied from 0.25 to 0.9 cc. without interference with the pupillary response to the alkaloid content.

Before examination the mice, which weighed 15 to 20 Gm., were kept in a quiet dark room. There the size of the pupils was measured with a Leitz preparation microscope (ultrapaque) equipped with an ocular micrometer and a constant light source. The pupillary size of both eyes was determined twice before treatment and twice forty minutes after injection of 0.001 and 0.002 mg. of atropine sulfate or 0.0005 and 0.001 mg. of scopolamine hydrobromide, and the averages were computed in a standard curve. Individual mice were not given another injection within a three day interval. Twelve groups of 5 mice each were standardized in this way.

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2. The electrode was prepared by Morris Graff, of the Department of Biochemistry.

3. van Heuven, J. A.: Ueber Glaukosan-Iontophorese, Arch. f. Augenh. **106**:625, 1932.

4. Pulewka, P.: Das Auge der weissen Maus als pharmakologisches Testobjekt: Eine Methode zur quantitativen Bestimmung kleinster Mengen Atropin und anderer Mydriatika, Arch. f. exper. Path. u. Pharmakol. **168**:307, 1932; Ueber die Wertbestimmung von Heilmitteln, welche atropinartige Stoffe enthalten (Zugleich II. Mitteilung über das Auge der weissen Maus als pharmakologisches Testobjekt), ibid. **180**:119, 1935.

5. Veit, F., and Vogt, M.: Die Verteilung von Arzneistoffen auf verschiedene Regionen des Zentralnervensystems, Arch. f. exper. Path. u. Pharmakol. **178**: 534, 1935.

6. Orzechowski, G., and Hundrieser, M.: Vergleichende Untersuchungen über Genalkaloide und entsprechende Alkaloide, Klin. Wchnschr. **15**:481, 1930.

The aqueous of the treated rabbit was injected into the test mouse directly after withdrawal from the anterior chamber. When a high concentration was expected, fractions of the aqueous were injected into 2 or 3 mice. The vitreous was centrifuged and the supernatant fluid measured and injected. An extract from the iris with ciliary body was prepared according to the technic described by Veit and Vogt [5] for brain tissue. The extraction was indicated for determination of the atropine and scopolamine adsorbed by tissue elements, especially those of lipoid nature. The method was slightly modified as follows: The iris and ciliary body were well ground together with 1 Gm. of quartz sand and 0.25 Gm. of sodium bicarbonate. They were then mixed with 0.5 Gm. of dehydrated sodium sulfate. After the material was dried it was pulverized and was placed in thimbles of a micro Soxhlet apparatus with a good reflux condenser and extracted for three hours with methylene chloride in a water bath at 70 C. The methylene chloride was then evaporated from small evaporating dishes in a warm water bath. The extraction flask was rinsed with 1 cc. of hot 0.3 per cent hydrochloric acid. The hydrochloric acid, with the residue in the evaporating dishes, was transferred to centrifuge tubes and heated in a boiling water bath with shaking for three minutes. After centrifuging, a light and sometimes slightly turbid fluid was obtained. The procedure was repeated two times, and the sediment was stirred with 1 cc. of hot hydrochloric acid after the rinsing of the evaporating dishes. The supernatant fluid of hydrochloric acid extract was then neutralized with sodium bicarbonate with warming. Measured amounts of the extracted fluid were injected into 2 or 3 mice.

Finally, readings for the animals given injections of aqueous, extract of iris with ciliary body and vitreous were plotted against the results obtained with standard solutions.

RESULTS

I. *Experiments with Atropine Sulfate.*—A. With the Corneal Route: In preliminray experiments it was found that the tonicity (hypotonicity or isotonicity) of the iontophoretically applied alkaloid salt solutions did not affect the results as it had been expected to in view of the theoretic calculations of Morisot,[7] Karbowski [8] and others. Hypotonic solutions of atropine sulfate in distilled water entered the eye by iontophoresis in concentrations similar to those of solutions made isotonic by the addition of sodium bicarbonate. The solutions of the atropine salt for the following series of experiments were therefore not made isotonic. They were applied in 0.1 and 0.25 per cent concentrations at 2 milliamperes for two minutes. The amounts in the aqueous and in the vitreous found one hour after iontophoresis were compared with those in the control eyes, which had been given a corneal bath with the same solution, tube and length of application. In the experiments with 0.1 per cent atropine sulfate solution, the amount of the alkaloid in the aqueous estimated by bioassay was six times more in the eyes

7. Morisot: L'iontothérapie en thérapeutique oculaire, Clin. opht. **32**:77 and 499, 1928.

8. Karbowski, M.: Iontophoresis in Ophthalmology, Ophthalmologica **97**: 166, 1939.

treated by iontophoresis than in the control eyes, as shown in table 1. When 0.25 per cent atropine sulfate solution was used, the concentration in the aqueous in the eyes treated by iontophoresis exceeded by nine times that in the control eyes. Table 1 also gives the readings obtained for the aqueous one hour after subconjunctival injection of 0.4 cc. of a 0.25 per cent solution of atropine sulfate. They are as low as those obtained with a simple corneal bath. The vitreous contains small amounts with all types of application. Because of the limitations of this bioassay method, the small differences in the low alkaloid content of the vitreous could not be evaluated. The iontophoretic introduction of the alkaloid with the technic described caused a transient opacity of the cornea of varying density but mostly of a moderate degree.

TABLE 1.—*Concentration of Atropine One Hour After Corneal Iontophoresis, Corneal Bath and Subconjunctival Injection*

Concentration of Atropine, Percentage	Form of Application	Length of Application, Minutes	Number of Experiments	Amount of Atropine in the Aqueous, Mg.	Amount of Atropine in the Vitreous, Mg.
0.1	Iontophoresis; 2 milliamperes	2	3	0.0025	Less than 0.0005
0.1	Bath	2	3	Less than 0.0005	Less than 0.0005
0.25	Iontophoresis; 2 milliamperes	2	4	0.0045	0.0003
0.25	Bath	2	3	0.0005	Less than 0.0005
0.25	Subconjunctival injection; 0.4 cc.	..	3	0.0005	0.00025

B. With the Transcleral Route at the Region of the Ciliary Body: In this series the concentration in the extract of iris with ciliary body was also measured. Atropine sulfate solution 0.25 per cent, alone or combined with a solution of epinephrine chloride 1:10,000, was applied with a slight increase in application time or amperage over that of the experiments with the corneal route. Epinephrine chloride was added because it was assumed that the abundance of the blood-filled vessels in the tissue reduces the concentration of the introduced drug. Control experiments with epinephrine chloride alone showed no effect on the pupil of the white mouse with the technic described.

As seen in table 2, the amount of the alkaloid in the aqueous with each solution was inconsistent and low and was similar to the amounts found with a two minute corneal bath. The concentration in the extract of iris with ciliary body was also low. The effect of the combination of atropine and epinephrine was evident in the readings for the aqueous as well as in those for the extract of iris with ciliary body, but the level did not approach that for the aqueous achieved with the corneal route.

C. With the Transcleral Route at the Equator of the Eye: These experiments were carried out in spite of the generally accepted opinion (Chatzky,[9] Steindorff,[10] Karbowski [8]) that ions cannot be introduced into the posterior segment of the eye through the vascular sponge of the choroid. This hypothesis had been disproved by previously reported experimental results with potassium sulfate and potassium rhodanide, in which the anions were driven into the vitreous through the sclera, choroid and retina.[11]

The results with atropine sulfate were not encouraging, as table 3 demonstrates, in regard to the concentration obtained in the vitreous.

TABLE 2.—*Concentration of Atropine One Hour After "Ciliary Body" Iontophoresis*

Concentration of Atropine, Percentage	Form of Application	Length of Application, Minutes	Number of Experiments	Amount of Atropine (Mg.) in		
				Aqueous	Ciliary Body	Vitreous
0.25	Iontophoresis; 3 milliamperes	2	3	0.00033	0.00016	0
0.25	Iontophorecis; 2 milliamperes; epinephrine chloride 1:10,000	3	6	0.0005	0.0005	0

TABLE 3.—*Concentration of Atropine One Hour After Scleral Iontophoresis*

Concentration of Atropine, Percentage	Form of Application	Length of Application, Minutes	Number of Experiments	Amount of Atropine (Mg.) in the	
				Aqueous	Vitreous
0.25	Iontophoresis; 2 milliamperes	2	3	0.00066	0.00016
1.0	Iontophoresis; 2 milliamperes	2	3	0.0013	0.00066
1.0	Iontophoresis; 5 milliamperes	5	3	0.002	0.00066

Solutions of atropine sulfate 0.25 and 1 per cent at 2 milliamperes for two minutes were used. In one series the milliamperage was increased to 5 and the length of application to five minutes. In experiments with the 0.25 per cent solution the amount estimated in the vitreous fluid was less than that obtained with corneal application. When 1 per cent solution was applied at 2 milliamperes for two minutes the content of the alkaloid in the vitreous was increased about four times. No further

9. Chatzky, cited by Morisot: L'ionothérapie appliquée aux affections oculaires, Clin. opht. **31**:5, 1927.

10. Steindorff, K.: Experimentelles zur Iontophorese, Arch. f. Ophth. **120**: 175, 1928.

11. von Sallmann, L.: Experimental Studies on Vitreous Detachment, Am. J. Ophth. **24**:1349, 1941.

increase over this concentration was obtained with a current of 5 milliamperes applied for five minutes.

II. *Experiments with Scopolamine Hydrobromide.*—In all experiments a 0.1 per cent solution of the alkaloid salt, an application time of two minutes and a current of 2 milliamperes were used. The alkaloid concentration in the aqueous, vitreous and iris with ciliary body was determined. The results are given in table 4.

A. With the Corneal Route: The reading of 0.004 mg. of scopolamine in the aqueous after an application of 0.1 per cent solution of the alkaloid salt is similar to that achieved with an application of 0.25 per cent solution of atropine sulfate at the same amperage and for the same length of time. The vitreous fluid contained about three times the amount of alkaloid found in the experiments with atropine. The extract of iris with ciliary body gave the high average reading of 0.003 mg.

TABLE 4.—*Concentration of Scopolamine One Hour After Corneal, Ciliary Body and Scleral Iontophoresis*

Concentration of Scopolamine, Percentage	Place of Application	Application		Number of Experiments	Amount of Scopolamine (Mg.) in the		
		Milliamperes	Time, Minutes		Aqueous	Ciliary Body	Vitreous
0.1	Cornea.....	2	2	4	0.004	0.003	0.0015
0.1	Ciliary body.....	2	2	4	0.001	0.0012	0.00017
0.1 (epinephrine chloride, 1:10,000)	Ciliary body.....	2	2	3	0.002	0.003	Trace
0.1 (epinephrine chloride, 1:10,000)	Sclera.....	2	2	3	0.0003	.....	0.00025

B. With the Transcleral Route in the Region of the Ciliary Body: In this group of experiments iontophoresis with 0.1 per cent solution of scopolamine hydrobromide was compared with iontophoretic application of a mixture of 0.1 per cent solution of scopolamine hydrobromide and 1:10,000 solution of epinephrine chloride. The addition of the epinephrine chloride to the scopolamine hydrobromide augmented the amount of the alkaloid two and a half times. The content of scopolamine in the extract of iris with ciliary body was about eight times more than that of atropine when a 0.25 per cent solution was used. When epinephrine was added to the scopolamine and the transcleral route used, the concentration in the extract of iris with ciliary body was the same as when the corneal route was used (0.003 mg.). The vitreous fluid contained very small amounts.

C. With the Transcleral Route at the Equator of the Eye: In this brief series of experiments only the combination of scopolamine hydrobromide and epinephrine chloride in a solution of 1:10,000 was studied,

and the concentration in the extract of iris with ciliary body was not determined. The content of the alkaloid in the vitreous fluid was higher than that in experiments with 0.25 per cent atropine sulfate solution but was about six times less than when the corneal route was used.

COMMENT

This experimental study is concerned only with the quantitative determination of atropine and scopolamine introduced into the eye by iontophoresis. Reference to the vast literature on iontophoresis in ophthalmology is omitted except for investigations immediately allied to this problem. Because of the complexity of the electrokinetic phenomena involved, with which must be associated the partially obscure factors in the simple penetration of drugs through the cornea, no attempt is made to analyze the mechanism of the procedure. Such an attempt would be of a purely speculative character.

The quantitative estimation of atropine and scopolamine in different parts of rabbits' eyes by means of bioassay, not previously used in ophthalmology, after iontophoresis and other forms of local application confirmed in general the clinical and experimental finding of Rochat and others that the effect of these drugs can be greatly increased when introduced by galvanic current. The content of the alkaloid in the aqueous one hour after iontophoretic treatment for two minutes at 2 milliamperes was found to be 0.004 to 0.0045 mg. when 0.1 per cent solution of scopolamine hydrobromide or 0.25 per cent solution of atropine sulfate was used. In general with stronger solutions greater amounts of the alkaloids are introduced, but no systematic experiments have been carried out for study of the relationship. Isotonicity of the alkaloid salt solutions did not result in the penetration of greater amounts.

The transient corneal opacity often found after treatment with the corneal technic was observed by Rochat in human beings receiving the same doses. It is not considered a contraindication, because of its transitory character, but Rochat was certainly correct in his injunction against doses higher than 1.5 milliamperes for two minutes. With his technic no signs of general intoxication were noticed by Rochat; on the contrary, he advised iontophoretic application in cases of atropine intoxication caused by the usual clinical administration. Experiments on rabbits do not throw any light on this question.

The figures for the examined parts of the rabbit's eye cannot be directly related to those for the human eye. The epithelium and stroma of the rabbit's cornea are somewhat thinner, and Bowman's membrane is not clearly developed. But the most essential difference affecting the penetration of drugs from a corneal bath with and without current is the diameter of the cornea, which measures 14 to 16 mm. in adult

rabbits. Nevertheless it is probable, and is suggested by clinical observation, that the relation between iontophoresis and other forms of application is essentially the same in the human eye as in the rabbit's eye.

Scopolamine hydrobromide, which has a higher specific velocity than atropine sulfate, penetrates by iontophoresis the cornea and deeper parts of the eye more readily. This fact was observed when the corneal route was used and also when the route through the conjunctiva and sclera to the ciliary body was employed. With the latter route and application of scopolamine hydrobromide with added epinephrine chloride, the same amounts were observed in the anterior part of the uvea as were found when the corneal route was used. No corneal opacity was observed with either of the transcleral methods.

One of the important problems in ocular therapy, the introduction of greater amounts of drugs into the posterior part of the eye, has not been solved by iontophoretic application. It is known from the experiments of Chatzky [9] that ions do not pass through circulating fluid, and it is assumed that they are carried away by such fluid. This explanation was also applied to the vascular sponge of the choroid. Whether it is correct or not, the amounts which passed through the sclera were moderate even in the presence of vascular constriction due to simultaneously administered epinephrine chloride.

The results were less consistent with both forms of transcleral application than with the corneal method, as was expected in view of the dense vascularization of the uvea and the difference in hyperemia due to treatment. Besides, the fluid in the ring tube in the ciliary body iontophoresis was sometimes not confined to the region of the ciliary body but leaked into the inner tube. Finally, it was difficult to control the placing of the tubes at the posterior circumference in both types of scleral application. On the other hand, the prevention of a corneal opacity was an advantage of the ciliary body iontophoresis, and the treatment with scopolamine hydrobromide combined with epinephrine chloride was as effective as the corneal method.

SUMMARY

1. The amounts of atropine introduced into the aqueous of rabbits by corneal iontophoresis at 2 milliamperes for two minutes were six to nine times greater than those introduced by a two minute corneal bath. Solutions of 0.1 and 0.25 per cent atropine sulfate were applied.

2. The atropine content of the aqueous of rabbits after subconjunctival injection of 0.4 cc. of a 0.25 per cent solution of atropine sulfate was nine times less than that following iontophoresis of the same solution at 2 milliamperes for two minutes.

3. Scopolamine applied in a concentration of 0.1 per cent of the hydrobromide salt entered the aqueous by the corneal route in amounts which approximated those of atropine applied in a concentration of 0.25 per cent of the sulfate salt. It penetrated better than atropine from the anterior chamber into the vitreous.

4. Transient opacities of the cornea were observed after corneal iontophoresis of each alkaloid salt at 2 milliamperes for two minutes. They corresponded to opacities observed after clinical use of the same technic. A transient opacity is not considered a contraindication for use of the method.

5. Experiments with two new transcleral methods of iontophoretic application failed in their main purpose, i. e., the introduction of greater amounts of alkaloid compounds into the vitreous. High concentrations of scopolamine in extract of the anterior part of the uvea were found after ciliary body iontophoresis with 0.1 per cent solution of scopolamine hydrobromide combined with 1 : 10,000 solution of epinephrine chloride.

Miss J. Di Grandi assisted throughout this study.

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OBJECTIVE STRABISMOMETRY IN YOUNG CHILDREN

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The modern trend toward earlier operation for the correction of strabismus has emphasized as never before the importance of measuring the amount of the deviation in young children. Today, many American ophthalmologists believe that under certain circumstances the operation can be done during the child's second year. It can be said with equal certainty that in many cases it is not only unnecessary but actually harmful to wait for the child to grow to an age at which intelligent cooperation can be obtained. For these reasons it seemed important to review the various methods of strabismometry that have been advocated, in an attempt to find the most accurate and practical means for estimating the deviation in these little patients.

HISTORICAL REVIEW

Prior to the middle of the nineteenth century, the textbooks of ophthalmology, as well as the treatises on strabismus, either failed to mention any measurement or else mentioned estimation of the degree by simple inspection. The following three grades of squint are typical of the teachings in those early volumes: "(1) The eye may be a little turned inwards, so that the deviation escapes notice without close observation; (2) the inner edge of the cornea may correspond to the internal canthus; (3) a part or nearly the whole of the cornea may be buried in the internal angle."[1] In other words, it served the purpose to decide whether a squint was slight, moderate or marked. In this connection it should be remembered that the first operation on an eye muscle was done in 1839. The same three degrees of strabismus were the only ones given by

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1. Lawrence, W.: Treatise on the Diseases of the Eye, Philadelphia, Lea & Blanchard, 1843, p. 715. Williams, W.: The Diseases of the Eye, ed. 3, London, H. G. Bohn, 1844, p. 772. Desmarres, L. A.: Traité théorique et pratique des maladies des yeux, Paris, Germer-Baillière, 1847, p. 782.

Deval [2] in 1862 and MacKenzie [3] in 1866, in spite of the advocacy of von Graefe, about 1857, of a more accurate method of determining the deviation.

Linear Measure.—Von Graefe was apparently the first to attempt a measurement of the amount an eye deviated in strabismus. His method was first described by Alfred Graefe,[4] as follows:

> Mark on the lower eyelid the point which corresponds to the vertical diameter of the pupil of the deviating eye; then, by excluding the other eye from vision, cause the patient to fix an object with the same eye and mark the point corresponding to the diameter of the pupil; the distance of these two points from one another is the linear expression of the deviation in question.

As primitive as this procedure may seem today, it was a tremendous step forward. Judging by the rapidity with which it came into general use, it apparently fell on fertile ground, no doubt prepared in large measure by the unfavorable results that were following tenotomies. It formed the basis for a school of thought that still has its exponents today. Alfred Graefe [5] later tried to reduce these measurements to a formula and suggested measuring from the limbus to the outer canthus when central fixation was absent.

Claiming that von Graefe's method was tedious as well as inaccurate, and not suitable in cases of amblyopia, Laurence [6] devised a strabismometer (fig. 1 *A*), which he described in 1865, after it had been in use for several years. This was probably the first instrument used to measure the degree of squint. It consisted of a small ivory plate curved to fit on the lower lid and marked in lines (later millimeters) to eliminate the marks made by von Graefe. Laurence described its object as being "to estimate the relative difference of position of the two eyes, rather than the individual absolute positions." Its simplicity and inexpensiveness have guaranteed its popularity to the present. A binocular instrument based

2. Deval, C.: Traité théorique et pratique des maladies des yeux, Paris, Albessard & Berard, 1862, p. 988.

3. MacKenzie, W.: A Practical Treatise on the Diseases of the Eye, London, Longmans, Green & Co., 1866, p. 353.

4. Graefe, A.: Klinische Analyse der Motilitätsstörungen des Auges, Berlin, Hermann Peters, 1858, p. 27 (footnote).

5. Graefe, A.: Motilitätsstörungen, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1880, vol. 6, chap. 9, p. 97; Motilitätsstörungen, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1898, vol. 8, chap. 11, p. 104.

6. Laurence, J. Z.: On Some Ophthalmic Instruments: A Strabismometer, Ophth. Rev. **1**:126-131, 1865; The Optical Defects of the Eye, and Their Consequences, Asthenopia and Strabismus, London, R. Hardwicke, 1865.

on the identical principle was contrived by Meyer [7] (fig. 1*B*). Adjustable needles could be made to indicate the center of each cornea simultaneously. This was undoubtedly an advantage over the monocular instrument, but its comparative complexity and expense kept the binocular instrument from ever seriously rivaling the Laurence strabis-

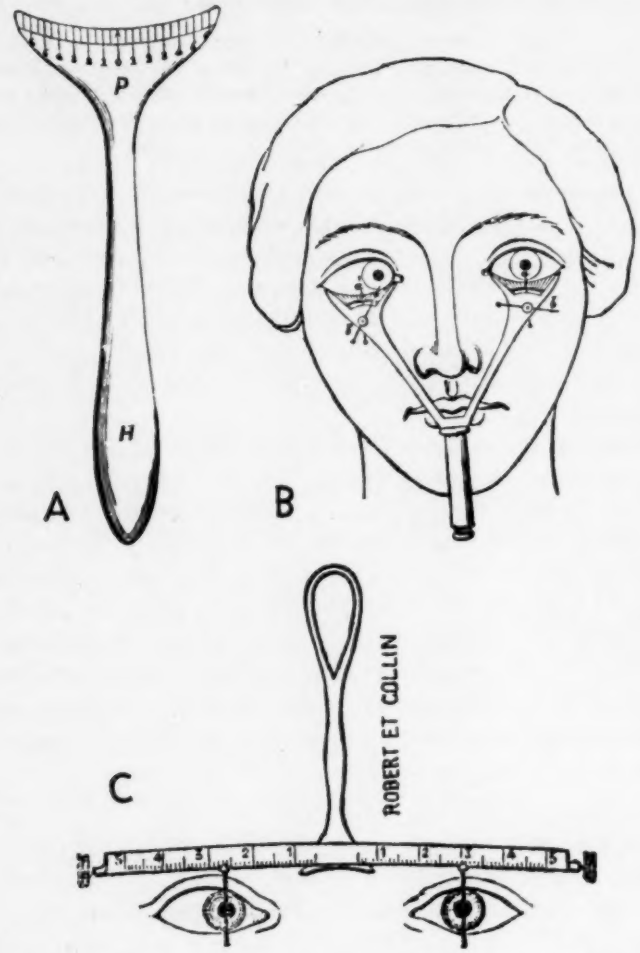

Fig. 1.—*A*, Laurence's strabismometer; *B*, Meyer's binocular instrument; *C*, Galezowski's binocular instrument.

7. Meyer, E.: Du strabisme et spécialement des conditions de succès de la strabotomie, Paris, Germer-Baillière, 1863; abstracted, Ann. d'ocul. **50**:329-334, 1863; Ein Instrument zur Messung des Schielgrades, Arch. f. Ophth. **9**:215-218, 1863.

mometer. In 1869 Galezowski [8] published a report on another binocular instrument (fig. 1*C*) for making linear measurements. It consisted of a horizontal bar held above the eyes. Two needles, projecting downward, could be moved laterally, by a screw at each end of the bar, to become alined with the centers of the corneas. The reading could then be made directly. This instrument would appear to be the most convenient of the early devices for linear measurements. Modern variants of the principle involved are to be seen in the instruments of Alcorn [9] (1933) and Smukler [10] (1939), which apparently offer only minor advantages. It is of considerable interest that even though Maddox [11] thought that this form of strabismometry had "quite gone out of favor" in 1892, it is still the method of choice for some modern ophthalmologists.

Angular Measure.—While there had been discussion as to the relative merits of linear and angular measurement of squint for several years, the first description found of an angular estimation was that by Steffan,[12] published in 1866 (fig. 2*A*). Holding the card (18 inches [46 cm.] square) horizontally in position before the squinting eye, Steffan moved a candle along the arc until the reflection was observed in the center of the cornea. Apparently this practical means for determining the deviation was never widely used. About the same time, Javal [13] utilized the perimeter to measure angle alpha, making use of the corneal reflexes. A little later Landolt [14] adapted the same principle for the estimation of the angle of squint (fig. 2*B*). With the deviating eye at the center of the perimeter, the patient was directed to fix either at a distance or at short range (*o*). A candle was then moved along the arc of the perimeter until its reflex was centered in the deviating cornea as seen by the observer immediately behind the candle (*x*). This maneuver gave a direct measure in degrees, but its accuracy was limited by the ability of the observer to estimate the center of the cornea. The limitation was serious and prompted Charpentier [15] to modify the method in 1878

8. Galezowski, X.: Strabomètre binoculaire, Ann. d'ocul. **61**:169, 1869.

9. Alcorn, J. G.: Linear Measurement of Strabismus; New, Simple, and Accurate Method, Am. J. Ophth. **16**:898, 1933.

10. Smukler, M. E.: Registering Deviometer: Instrument to Measure Degree of Squint, Arch. Ophth. **22**:881-882 (Nov.) 1939.

11. Maddox, E. E.: Objective Strabismometry, Arch. Ophth. **21**:56-62, 1892.

12. Steffan, P.: On the Estimation of the Amount of Deviation of a Squinting Eye, Ophth. Rev. **2**:331-334, 1866.

13. Javal, E.: Du strabisme, Ann. d'ocul. **66**:113, 1871.

14. Landolt, E.: Sur la strabométrie, Ann. d'ocul. **74**:61-74, 1875; translated, Ann. di ottal. **4**:478-489, 1875. Ophthalmotropométrie, in de Wecker, L., and Landolt, E.: Traité complete d'ophthalmologie, Paris, A. Delahaye et Cie, 1878, vol. 1, p. 910.

15. Charpentier, A.: Nouveau procédé pour déterminer l'angle du strabisme, Ann. d'ocul. **79**:30-52, 1878.

(fig. 2C). Instead of the candle being moved along the arc, the light was kept at the center of the perimeter (*L*), while the observer moved his eye along the arc until the candle appeared to be centered in the squinting cornea (*B*); then he divided the reading by two to get the angle of deviation (*A*). This method was more accurate for small deviations,

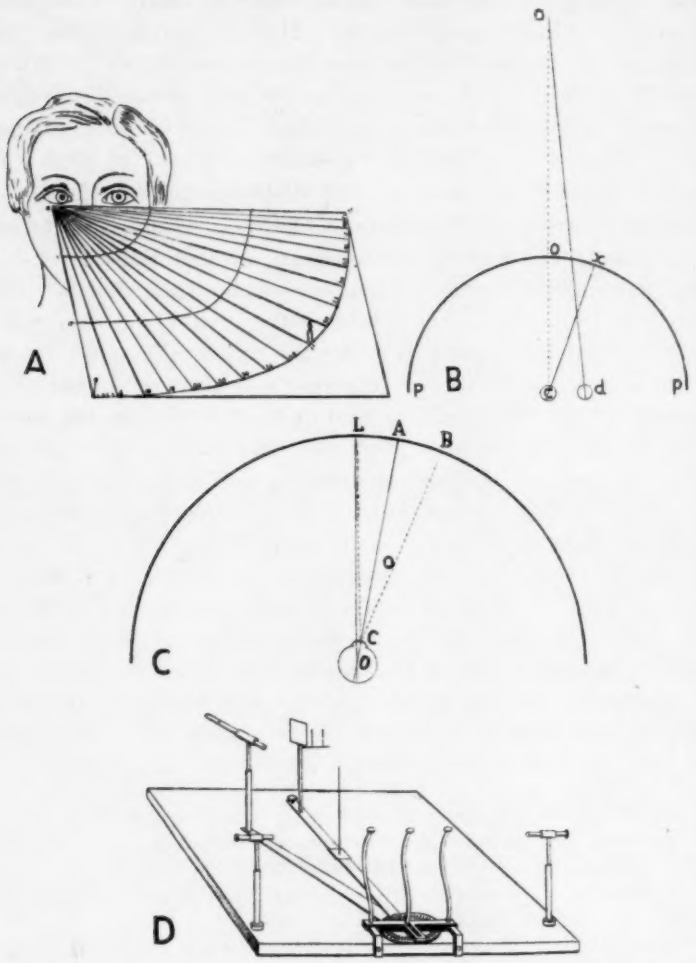

Fig. 2.—*A*, Steffan's method of angular estimation; *B*, Landolt's method; *C*, Charpentier's method; *D*, Snellen's ophthalmotropometer.

and the observer was not disturbed by the flame directly in front of his eye, but it could not be used in measuring large convergent squints, because of the interference of the nose.

Finding that the perimeter took too much time, that it was hard to keep the eye at the center of the perimeter and that a deviation greater

than the arm of the perimeter could not be handled, Snellen [16] devised his ophthalmotropometer in 1873 (fig. 2*D*). The deviating eye was placed above the central pin, around which two arms rotated on a protractor marked in degrees. One arm carried various devices for maintaining fixation, while on the other was mounted a small telescope to center it on the deviating eye. This instrument was undoubtedly more accurate than the perimeter but also more complex, and it had the serious drawback of being limited to measurements in the horizontal plane. Another device for making angular measurements was the *arc keratoscopique* of de Wecker and Masselon [17] (1884). This was a small hand perimeter (fig. 3*D*) with a 15 cm. radius, of which the arc was movable laterally. On this arc were mounted two white disks, one 70 degrees to each side of the center, so placed that when the arc was centered on the cornea, a reflex fell near the limbus on each side. This instrument added materially to the precision with which the center of the deviating cornea could be found. As compared with the ordinary perimeter, its increased accuracy, combined with its convenience and simplicity, made it an extremely valuable piece of apparatus. Its chief drawback was the short radius of the arc.

Working on the same principle, the location of the corneal images, Priestley Smith [18] reported on his famous tape measure in 1888 (fig. 3*A*). Using the ophthalmoscope mirror as his source of light, he placed a ring around its handle and attached two tapes to it (*o*), each 1 meter long. The first tape extended to the patient and was held under the squinting eye (*P*). The second tape was held at right angles to the first so that it constituted a tangent. After noting the location of the reflex in the fixing cornea, Smith asked the patient to follow his finger (with the fixing eye) as he carried it along the second tape until the reflex reached a symmetric position in the squinting cornea. This tape could be made from materials to be found in most households, could be carried in the pocket, was extremely easy to use and was just as accurate as the perimeter. These features were responsible for its rapid acceptance by the medical profession. Holzer [19] in 1919 made a valuable modification by

16. Snellen, H.: Ophthalmotropometer, Klin. Monatsbl. f. Augenh. **11**:424, 1873; translated, Ann. d'ocul. **71**:275, 1874; in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1874. vol. 3, chap. 1, pp. 235-237.

17. de Wecker, L., and Masselon, J.: L'arc kératoscopique, son emploi comme kératoconomètie, pupillométre et strabomètre, Rev. clin. d'ocul. **4**:201-209, 1884; Manuel d'ophthalmologie, Paris, Lecrosnier & Babé, 1889, p. 758; La strabométrie et l'urgence de son emploi, Ann. d'ocul. **114**:321-336, 1896.

18. Smith, P.: A Tape-Measure for Strabismus, Ophth. Rev. **7**:349-352, 1888.

19. Holzer, W. F.: Determination of Deviation in Squint by the Priestley Smith Method with a Modification to Insure Greater Accuracy, Am. J. Ophth. **2**:520-522, 1919.

shortening the first tape to 60 cm. and adding a third tape of the same length, united with the first, at the patient's eye (*A*, fig. 3*B*). The second tape slides through a ring at the other end of the third (*C*) and has a weight added to its free end to keep it taut. This creates an isosceles triangle with its apex at the squinting eye (*A*), so that every centimeter on the second tape equals approximately 1 degree. Thus he improved the convenience of the tape without appreciably reducing its accuracy. Later Wilkinson [20] replaced tape 1 with a light piece of wood, and finally Alvaro [21] made both 1 and 3 rigid, with a hinge at the squinting eye.

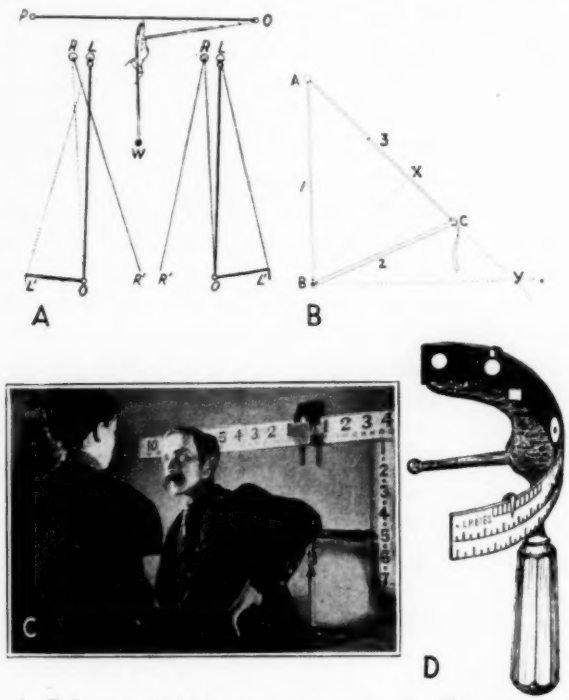

Fig. 3.—*A*, Priestley Smith's tape measure; *B*, Holzer's modification; *C*, Maddox's tangent scale; *D*, de Wecker and Masselon's *arc kératoscopique*.

This tape, or one of its modifications, is described in all modern textbooks and is extensively used.

In 1890 Maddox described the use of his tangent scale, which is best known as a subjective test. However, the scale can be used as a flat

20. Wilkinson, O.: Strabismus: Its Etiology and Treatment, St. Louis, C. V. Mosby Company, 1927, p. 116.

21. Alvaro, M. E.: Squint Measurement with Priestley Smith's Improved Method, Am. J. Ophth. **18**:143-145, 1935; Apparelhagem para a medicao exacta do estrabismo, Cong. argent. de oftal. **1**: 392-400, 1936; abstracted, Zentralbl. f. d. ges. Ophth. **41**:175, 1938.

perimeter, as shown in figure 3*C*. The patient is directed to look along the scale with his fixing eye until the reflection of the light, at zero, is centered in the squinting cornea. Its chief advantage lies in its availability and economy of space. Similar to Snellen's ophthalmotropometer, but more elaborate, was an instrument devised by Sattler and Herring. This was described by Bielschowsky [22] in 1897. As shown in figure 4 *A*, this apparatus is the most complicated and undoubtedly the most expensive one that has been encountered for the measuring of squint. The head was maintained in a central position by means of a forehead rest, and a separate arm was provided for each eye in addition to the one for fixation. Two gas flames produced double corneal images, which were located with the aid of a telescope, the examiner sighting between them on the same arm. This was surely a precision instrument but hardly one for routine clinical use. In the first edition of his book on squint (1903), Worth [23] described his deviometer (fig. 4*B*), for which he claimed rapidity and accuracy. This instrument was really another flat perimeter. The arm could be swung to either side and the white fixation spot moved along it. It is the first apparatus in which an electric light was used; this was placed at the center. It is difficult to see what advantages the apparatus had over the ordinary perimeter. Howe [24] added a strabometer in 1906. The bar (fig. 4*D*), which rotated on a protractor, was equipped with gun sights to line it up with the deviating eye. This instrument should have been a convenient one to use, but it would seem to be almost impossible to keep the zero mark on the protractor parallel to the visual axis of the fixing eye. More recently, Bressler [25] (1934) presented a greatly trimmed-down perimeter which should definitely facilitate observations. And, finally, Sergeev [26] (1939) improved the perimeter for strabismometry by attaching a fixed light at the center and a movable light on the arc.

Almost before a satisfactory method for making angular measurements had been devised, a controversy arose over the relative merits of the linear and angular determinations. This continued with considerable warmth on both sides through most of the latter half of the nineteenth

22. Bielschowsky, A.: Demonstration eines neuen Apparates zur Messung des Schielgrades, Ber. ü. d. Versamml. d. ophth. Gesellsch. **26**:262-264, 1897.

23. Worth, C.: Squint, Its Causes, Pathology and Treatment, Philadelphia, P. Blakiston's Son & Co., 1903.

24. Howe, L.: Muscles of the Eye, New York, G. P. Putnam's Sons, 1908, vol. 2, p. 178.

25. Bressler, J. L.: A Strabismometer, Tr. Sect. Ophth., A. M. A., 1934, p. 298.

26. Sergeev, I. V.: Determination of the Angle of Manifest Strabismus, Vestnik oftal. **15**:86-87, 1939; abstracted, Am. J. Ophth. **23**:229, 1940.

century. Von Graefe [27] was conspicuous among the advocates of the linear method. He thought that "one should not try to be too exact in measurement because of the variations in the position of the eye" and "because of the inconvenience in practice attending the measurement of

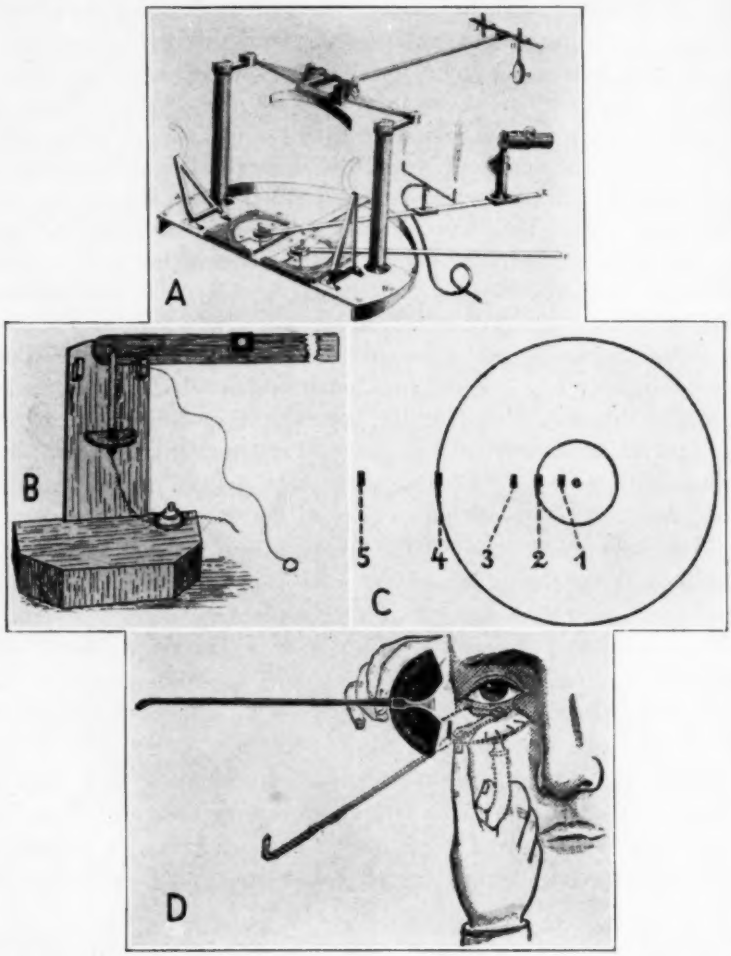

Fig. 4.—*A*, Sattler and Herring's apparatus; *B*, Worth's deviometer; *C*, Hirschberg's corneal reflex; *D*, Howe's strabometer.

angles." Alfred Graefe was more radical in stating his belief in "the much greater exactitude of the linear, in comparison with the angular"

27. von Graefe, A.: Beiträge zur Lehre vom Schielen und von der Schiel-Operation, Arch. f. Ophth. **3**:177-386, 1857; Recherches sur le strabisme et les opérations qu'il réclame, Ann. d'ocul. **45**:85, 1861.

measurements, and in this he was almost unique. Javal [28] wrote that "exact measure is useless because of the continual variations in the degree of the deviation." And there were others,[29] most of whom agreed that the angular method was more exact but not worth the effort. The linear was the only method described in the first and second American editions of Fuchs's textbook, in 1892 and 1899.[30] On the other side of the argument were Snellen, Landolt, de Wecker, Priestley Smith and Maddox, to name only a few who claimed that exactness was important. The argument is not yet ended, as supporters for both sides are still to be found.

Hirschberg Method.—Somewhat between the two concepts of linear and angular measurement lies the important contribution of Hirschberg,[31] in 1885. Holding a candle at 12 inches (30 cm.), he observed the position of the reflex in the cornea of the deviating eye. He divided all cases into five groups (fig. 4*C*): those in which the reflex is (1) nearer to the center than to the pupillary margin, i. e., 5 to 6 degrees; (2) at the pupillary margin (pupil 3 mm.), i. e., 12 to 15 degrees; (3) halfway to the limbus, i. e., 25 degrees; (4) at the limbus, i. e., 45 to 50 degrees, and (5) beyond the limbus, i. e., 60 to 80 degrees. He did not describe making his examination with distance fixation, and it is probable that he did not attempt to do it routinely. It is practically impossible for the observer to get his head and a light in position for satisfactory observation while the patient is fixing at a distance. Hirschberg's method required a minimum of equipment, and with a little experience it was at least as accurate as the linear methods. It was particularly useful for young children. It soon gained wide popularity, which has been maintained to the present, although today it is reserved chiefly for the very young.

Screen Test.—Duane [32] first published the screen test in 1889, yet it was included only in the appendix of the third edition of Fuchs's famed

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28. Javal, E.: Manuel théoretique et pratique du strabisme, Paris, G. Masson, 1896, pp. 55 and 59; reviewed by Zehender, W.: Klin. Monatsbl. f. Augenh. **34**:207-210, 1896. Javal.[13]

29. Berry, G. A.: The Determination of the Degree of Latent and Manifest Squint in Meter Angles: A Suggestion, Ophth. Rev. **3**:193-202, 1884. Schweigger, E. T. C.: Handbook of Ophthalmology, English translation, Philadelphia, J. B. Lippincott & Co., 1878, p. 155. Walton, H.: A Practical Treatise of the Diseases of the Eye, ed. 3, London, J. & A. Churchill, 1875, p. 369.

30. Fuchs, E.: Text-book of Ophthalmology, English translation, ed. 1, New York, D. Appleton and Company, 1892, pp. 535, 563 and 572; ed. 2, 1899; ed. 3, Philadelphia, J. B. Lippincott & Co., 1908, p. 676; ed. 5, 1917, p. 767.

31. Hirschberg, J.: Ueber Messung des Schielgrades und Dosirung der Schieloperation, Centralbl. f. prakt. Augenh. **9**:325-327, 1885; Beiträge zur Lehre von Schielem und von der Schieloperation, ibid. **10**:5-9, 1886.

32. Duane, A.: Some New Tests for Insufficiencies of the Ocular Muscles, Together with a System of Abbreviation Suitable for Notetaking, New York

(Footnote continued on next page)

textbook, which Duane translated, and not until the fifth edition (1917) did it receive a place in the chapter on ocular motility. Duane must be given full credit for this valuable addition to the ophthalmologist's armamentarium, which, through the continued efforts of White,[33] Dunnington [34] and others,[35] has gradually gained in popularity, until today it is the method of choice of the majority of the persons teaching this branch of ophthalmology. Duane [36] described his way of making the test as follows:

> The patient is directed to fix the object sharply, a card is passed from one eye to the other, and the deviation of the eye behind the screen (or the opposite movement of redress when the eye is uncovered) is noted. Prisms are then placed before one eye in such a way as to correct the deviation, and are added until the deflection is not only abolished but reversed.

In comparing the screen test with use of the perimeter, the Smith tape and the Hirschberg test, Duane concluded:

> No one of these methods at all approaches the screen test either in accuracy or in convenience. Nor do they show, or at least they show very imperfectly, the character of the squint. Nor can they measure a vertical and a lateral simultaneously, as the screen test does. Nor can they measure well, as it does, low degrees of squint and they cannot measure heterophoria at all. Nor can they show, as it does, the varying amount of the deviation in different directions of gaze. Add to this the fact that the application of the screen test is extremely simple and requires no apparatus whatever but a few prisms, that it can be applied readily in children, that it can be used in cases of paralysis to show the amount of primary and secondary deviation, and finally that it is the easiest and most accurate means of checking the result in an operation and I think it clear why I should advocate its use as a routine method at the exclusion of the other means of measuring deviations.

M. J. **50**:113-118, 1889; A New Classification of the Motor Anomalies of the Eye, Based upon Physiological Principles, Ann. Ophth. & Otol. **5**:969-1008, 1896; **6**:247-260, 1897; reprinted, New York, J. H. Vail & Co., 1897; The Value of the Screen Test as a Precise Means of Measuring Squint, Ann. Ophth. **12**:620-630, 1903.

33. White, J. W.: (*a*) Routine Muscle Examination in Its Practical Application, Tr. Sect. Ophth., A. M. A., 1934, pp. 160-171; (*b*) The Screen Test and Its Application, Am. J. Ophth. **19**:653-659, 1936; ((*c*) Macular Anomalies and Ametropia: Practical Consideration, Arch. Ophth. **18**:892-896 (Dec.) 1937; (*d*) What Is the Minimum Routine Examination of Muscles? ibid. **24**:1113-1122 (Dec.) 1940; (*e*) Screen Test and Its Modifications, Screen-Maddox Rod and Screen Comitance, Am. J. Ophth. **24**:156-160 (Feb.) 1941.

34. Dunnington, J. H.: Diseases of the Extra-Ocular Muscles, in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1937, vol. 11, chap. 13, pp. 303-328.

35. Lancaster, W. B.: Detecting, Measuring, Plotting and Interpreting Ocular Deviations, Arch. Ophth. **22**:867-880 (Nov.) 1939. Berens, C.; Losey, R. R., and Hardy, L. H.: Routine Examinations of Ocular Muscles and Non-Operative Treatment, Am. J. Ophth. **10**:910-918 (Dec.) 1927.

36. Duane, A.: Motor Anomalies of the Eye: The Relative Value of the Tests Used in Diagnosing Them, New York M. J. **99**:409-416, 1914.

Finally, there is his one criticism of the test:

> The screen test fails whenever one of the eyes cannot be made to perform central fixation. This occurs mainly in eccentric fixation due to a large central scotoma or in high grade amblyopia or actual blindness of one eye.

Apparently Duane did not consider young children, as no mention was found of the inapplicability of the test to this group. While White has shown that with patience and repeated trials the screen test can be used successfully on some 3 year olds, this is not universally true, and there is a large number of young patients on whom it cannot be used.

Use of the Synoptophore.—The synoptophore, brought out by Ettles in 1914, and the similar, later instruments, the synoptiscope and the orthoptoscope, collectively termed "major amblyoscopes," can be used to measure strabismus objectively. The test is usually made with dissimilar slides, such as the lion before one eye and the cage before the other. With the flash buttons used alternately, the patient is shown first one picture and then the other, and at the same time the tubes are moved (angular displacement) until there is no more movement of the eyes. The measurement of the deviation can then be read off the scale in either degrees or prism diopters. This test is essentially a screen test. The closeness of the targets to the eyes causes a psychologic stimulation of accommodation, which tends to give a slightly higher reading in convergent squint. This takes place in spite of lenses in the instrument that correct for infinity, and is frequently called "apparatus convergence." Making this test on the synoptophore is a routine procedure for an orthoptic technician, requiring only a few moments. Its two disadvantages, as compared with the screen test, are the high cost of the instrument and the nuisance of adjusting it to the patient.

COMMENT

While the perimeter and the Priestley Smith tape are probably the most widely used instruments for measuring the deviation in this country, the screen test is rapidly gaining advocates. White [33b] gave the following three reasons for its slow adoption:

> First, Duane wrote so completely and scientifically concerning the test that it seemed too difficult to many, hence they looked for something more simple. The test as made by him in his office, however, was simplicity itself.
>
> Second, the test needed no expensive instruments and the instrument houses had expensive instruments for sale before which a patient could be seated. By turning a few levers, the diagnosis and treatment (almost) would be stamped on the history card. Hence, the screen test received no advertising, but instead was ignored.
>
> Third, the test needed experience in making the examination and a knowledge of the underlying principles of the motor apparatus of the eyes which seemed to be unnecessary in the other methods.

It would seem a fair statement that a majority of authorities are in agreement with Duane that the screen test gives the most accurate measure of the deviation, as well as the most complete picture of the condition, and at the same time is the simplest of execution. There are, however, two important limitations; namely, that the patient must have central fixation in both eyes and that he must be old enough to cooperate. These requisites immediately eliminate two large groups of patients, the very young and those with amblyopia, so that additional methods of measurement are required. For amblyopic patients, some variation of the angular determination from the corneal reflexes offers the greatest precision. Of these, use of the *arc keratoscopique* of de Wecker and Masselon is probably the most accurate without being too complicated, while the Hirschberg test is undoubtedly the easiest to use. Midway between these two as to accuracy and convenience is use of the Holzer modification of the Smith tape. The great majority of very young patients will fix a light, but many will submit to nothing more than this, so that a test like Hirschberg's is the only one that can be employed. This opinion has been expressed by Maddox,[11] White [33d] and others.

THE PROBLEM

Since nothing that has been published appeared to suit the problem of the very young patient with strabismus as well as the fifty-five year old Hirschberg test, it was decided that this test should be subjected to a careful reappraisal. On repeated occasions, I had been impressed by a definite discrepancy between the apparent deviation (Hirschberg) and the actual measurement with the screen test, so that a recheck of Hirschberg's values was in order.

The first problem was to recheck Hirschberg's original observations. His figure for the average horizontal diameter of the cornea, 12 mm., could be accepted. Hirschberg checked his measurements in cases of double vision. This procedure was not repeated, because of the rarity of cases in which it could be done accurately. He also checked his figures by observing the corneal reflexes of normal eyes at various positions on the perimeter. This experiment was repeated, and the reading for the external limbus was found to vary from 40 to 55 degrees, with the average about 48 degrees. A reading at the limbus can be made with reasonable accuracy, but no method has been found that will locate the intermediate steps on the cornea with precision. Attempts to show these steps photographically have been made by Chavasse [37] and Gibson [38] with

37. Chavasse, F. B.: Worth's Squint, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1939, p. 429.

38. Gibson, G. G.: An Analysis of Operative Results for Concomitant Convergent Strabismus, Arch. Ophth. **23**:447-486 (March) 1940.

fair success, but the photographs are not susceptible to quantitative measurements. While the pupil and iris cannot be ignored, my experience has indicated that the best procedure is to divide the temporal radius of the cornea, "by eye," into two, three or six equal parts and to allow 8 degrees for each millimeter. With practice, the estimates become fairly reliable.

To check the Hirschberg test against other widely used procedures, in actual cases, the following problem was undertaken. Cases were selected which fulfilled these three requirements: (1) there was a frank deviation, (2) there was reliable central fixation in each eye and (3) the patient was old enough to cooperate in the screen test. Measurements were made in these cases by the following five methods: (1) Hirschberg method, (2) linear measure, (3) angular measure, (4) screen test and (5) use of the synoptophore. Since the Hirschberg test was on trial, it was done first to avoid prejudice. All the measurements were made by me.

Linear Measure.—The Laurence instrument was given a trial and proved to be unsatisfactory because of the distance of the rulings from the corneal reflex. In its place I found that a 5 cent transparent millimeter ruler was far more accurate. When the ruler was held close to the eye with its upper edge on the horizontal diameter of the cornea, the reflex fell along this edge. With the light held at 12 inches (33 cm.) directly in front of the patient, the distance of the corneal reflex from the lateral limbus was measured in each eye and the difference recorded. A similar transparent measure, attributed to Aubaret, was later found in Cantonnet's [39] book. As might be expected because of their identical basic principles, observations with the Hirschberg test and with the ruler produced results within 0.5 mm. of each other in 97 per cent of the cases. With experience on the part of the examiner, they became practically identical. It was found that 0.5 mm. was the smallest displacement that could be appreciated.

Angular Measure.—Both the Holzer modification of the Smith tape and the perimeter were used until I was convinced that the latter offered no advantage over the tape. I found that the tape was more accurate, owing to the greater distance at which the reading was made, and it was far easier for both the examiner and the patient. The angle between the central pupillary line and the visual axis, angle kappa (Duke-Elder [40]), was assumed to be symmetric in the two eyes because there is no conceivable way to measure it in small children. In order to compare the

39. Cantonnet, A.; Filliozat, J., and Fombeure, G.: Le strabisme, Paris, N. Maloine, 1932, p. 196.

40. Duke-Elder, W. S.: Text-Book of Ophthalmology, London, Henry Kimpton, 1932, vol. 1, pp. 681 and 760.

Hirschberg figures with the tape measurements, the former were transposed into angular values by the arbitrary rule that 1 mm. equals 8 degrees (see accompanying table). The tape gave higher readings for 75 per cent of the cases (the greatest difference being 13 degrees) and

Comparative Measurements Obtained with the Hirschberg, Tape and Screen Tests in Cases of Strabismus

Tape	Difference*	Hirschberg	Difference*	Screen
4	0	4	2	6
10	2	8	3	11
		8	6	14
10	2	8	6	14
7	1*	8	8	16
12	4	8	8	16
15	3	12	4	16
15	1*	16	0	16
10	2	8	11	19
18	6	12	7	19
25	9	16	3	19
20	0	20	2	22
		24	0	24
10	2	8	18	26
20	4	16	10	26
25	9	16	10	26
25	9	16	10	26
18	6	12	16	28
15	1*	16	12	28
22	6	16	12	28
30	10	20	8	28
		36	8*	28
28	12	16	14	30
25	5	20	13	33
35	11	24	9	33
20	0	20	15	35
25	5	20	15	35
35	11	24	11	35
40	8	32	3	35
40	12	28	9	37
35	1*	36	1	37
40	4	36	3	39
32	4*	36	10	46
45	3*	48+	2*	46
45	13	32	16	48

* The differences indicate that the Hirschberg measurement is smaller except as marked with an asterisk. The figures have been reduced to degrees of arc; those for the screen test are given in the nearest even number according to the scale of Duke-Elder.[40]

lower for 16 per cent, and the average was 4.5 degrees higher. The tape should be more accurate, because it is a question of moving the squinting eye, by means of the fixing eye, until the corneal reflex assumes a central (or symmetric, where there is an angle kappa) position. This is a simpler determination than estimating a distance on the cornea. No explanation has been found for the higher reading with the tape.

Screen Test.—The values in prism diopters obtained in the screen test were reduced to degrees of arc according to the method of Duke-Elder [40] (see table). The Hirschberg measurement was larger in

only 2 instances, in 1 of which the reflex fell outside of the limbus. The measurements were equal in 2 and in 8 were within 4 degrees, which has been designated as the probable error of the Hirschberg test. This left 23 cases (66 per cent) in which the measurement with the screen test was greater than that with the Hirschberg test by from 6 to 18 degrees, an average difference of 11 degrees. A difference of this magnitude in two thirds of the cases would seem to indicate that the tests are measuring different things. From my experience with the Hirschberg test, checking normal eyes on the perimeter and squint by methods of Javal, Charpentier and Priestley Smith, I am satisfied that the Hirschberg test gives a true, if approximate, expression of the angle at which the nonfixing eye deviates from the primary (fixing) position. This might be called the static angle. The screen test, on the other hand, does not attempt to measure the static angle, but rather it determines the amount of prism that is required to prevent movement of the eyes as they take up fixation alternately, the nonfixing eye being in a nonseeing position behind the screen. One possible explanation for this difference in the values obtained with the two tests could be that the screen measures more than the Hirschberg test. Since the latter has been shown to express the manifest deviation, the screen test must give the manifest angle plus something more, which might be called a phoria component. This concept is consistent with the nature of the screen test, and no objection to it has been found. White [33b] suggested it when he said, "The screen test measures more nearly the total amount of deviation, while other tests measure only the amount that cannot be overcome, or the amount that the deviation is increased by the convergence action in binocular vision," but he did not enlarge on it. Further analysis of the data in these cases failed to show any relationship between the age, amblyopia or refractive error and the difference between the two tests.

The clinical significance of this difference will require further investigation. The question of which test represents the amount that should be corrected by operation is of prime importance. For a cosmetic cure, the manifest angle should be sufficient. For a functional cure, it may be necessary to correct the entire deviation. The relation this may have to the permanence of the operative result will have to wait for an analysis of a large series of surgical cases.

Use of Synoptophore.—Satisfactory measurements were obtained on the synoptophore in only 12 instances. Since the test with this apparatus so closely resembles the screen test, the figures from the two were compared. The values obtained with the synoptophore averaged 2.2 degrees higher. As previously explained, the difference was probably due to "apparatus convergence." The diagnosis of abnormal retinal correspondence was made in 8 of the 12 cases in which measurements were made on the synoptophore. In 6 of these 8 cases, a large difference was found

between the objective measurements obtained by the Hirschberg test and with the synoptophore (average, 13.5 degrees). These figures are too few to be more than suggestive.

CONCLUSIONS

1. The Hirschberg test is the best one available for measuring the deviation in young children.

2. The original values given this test are still approximately correct. No way has been found to increase its accuracy.

3. The screen test gave significantly higher readings in two thirds of the cases studied, an average of 11 degrees.

4. This difference is believed to be an expression of the different fundamental principles of the two tests rather than an error in either.

5. The Hirschberg test is a true if approximate measure of the static angle of deviation; the screen brings out this manifest deviation plus a phoria component.

6. The clinical significance of this difference must await further investigation.

30 West Fifty-Ninth Street.

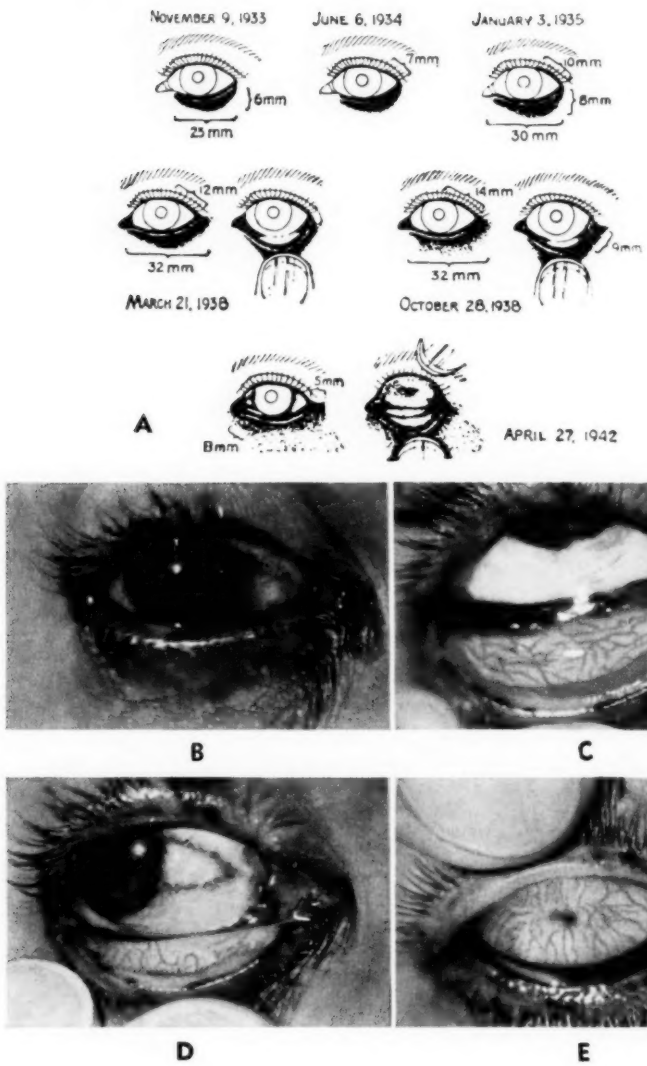

Fig. 1.—A man aged 50 first noticed a pigmented spot about the size of a pinpoint along the margin of the left lid in 1915. By 1927 it was about the size of a pinhead. There was further enlargement, so that in 1932 a biopsy was performed; this showed precancerous changes. The lesion steadily progressed and the patient refused treatment. The sketches in *A*, drawn to scale, show the progression from November 1933 to April 1942. In May 1942 kodachrome slides were made as follows: *B*, pigmentation of the upper and lower lids and the bulbar conjunctiva; *C*, pigmentation of the lower palpebral conjunctiva, fornix and bulbar conjunctiva, shown with the lower lid pulled down; *D*, pigmentation of the upper and lower lids, bulbar conjunctiva, caruncle and semilunar fold, shown with the lower lid pulled down; *E*, pigmentation of the upper and lower lids and the upper palpebral conjunctiva, shown with the upper lid everted. At no site is there any elevation of the tumor, except perhaps in the lower fornix. The tumor is in the malignant phase, and exenteration should have been done at a much earlier period.

UNIV. OF MICH.

PRECANCEROUS MELANOSIS AND THE RESULTING MALIGNANT MELANOMA (CANCEROUS MELANOSIS) OF CONJUNCTIVA AND SKIN OF LIDS

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In 1938 I [1] reported on precancerous melanosis of the conjunctiva and skin of the lids and on the type of malignant melanoma (cancerous melanosis) to which this melanosis gives rise. The purpose of the present report is to record further observations on these acquired conditions and to discuss their relationship to the congenital nevus and the malignant melanoma which may arise from it.

Precancerous melanosis is a diffuse, nonelevated pigmentation which has a granular appearance, with sometimes a slight loss of luster of the involved conjunctival surface. The average age at which it appears is from 40 to 50 years, and the average length of time between its appearance and the malignant change is from five to ten years. The interval may be a great deal longer or considerably shorter, however, and at times the melanosis is malignant from the beginning. An important characteristic is its diffuseness. The lesion may become so diffuse as to involve almost all the bulbar and palpebral conjunctiva and adjacent skin without causing any localized tumor mass. Malignant areas may make their appearance at any site, and they usually appear at many sites either simultaneously or at irregular intervals in the course of the disease. They may remain flat, as in the precancerous stage, or they may become somewhat elevated. If the tumor is allowed to grow unheeded it may ultimately manifest itself in localized tumor masses, but it usually remains flat and may involve the entire bulbar and palpebral conjunctiva and terminate fatally by metastasis without forming an elevated mass (fig. 1). Extensive involvement of the conjunctiva and skin results, not from spread by direct continuity from one malignant site, but rather from multiple scattered foci in a diffuse, widespread precancerous melanosis.

HISTOLOGIC CHANGES

The earliest changes appear in the cells of the basal layer. These increase in number and become pigmented, swollen, hydropic and sep-

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1. Included is a case of Dr. Brittain Payne's.

arated from one another by clear spaces (fig. 2, *a*). The swelling gives a large protoplasmic element to the cells, which may be clear or may show an amorphous granular content interspersed with varying numbers of pigment granules. Some cells show an enormous globular distention associated with degeneration of the nucleus, which stains poorly and assumes a granular appearance. Several or many adjacent swollen cells may become confluent, forming clear spaces containing the degenerative products of the involved cells. The protoplasm of the less swollen cells may be finely granular or honeycombed and may contain

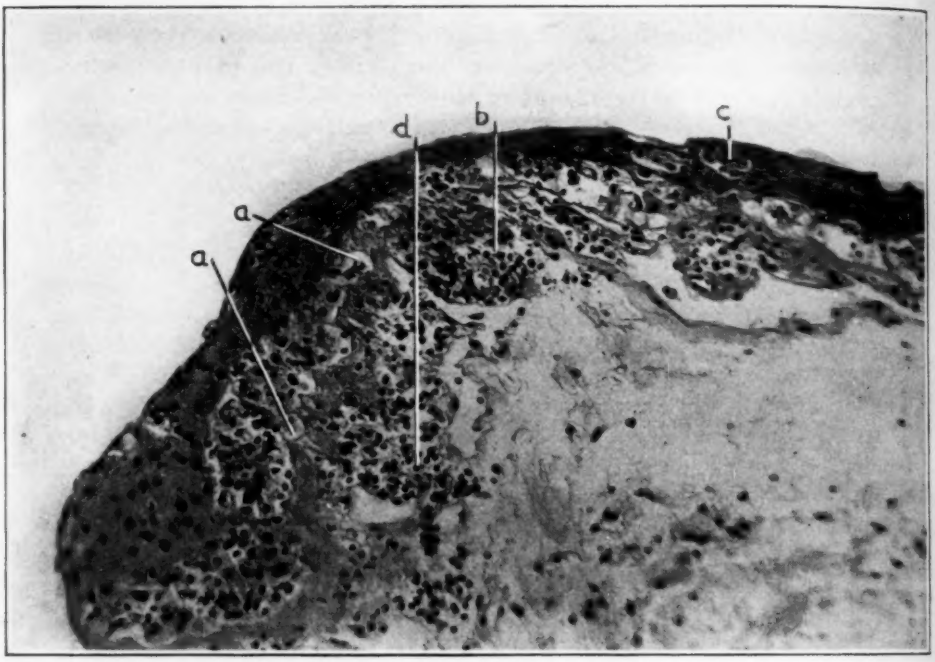

Fig. 2.—A section of tissue removed for biopsy in a case of precancerous melanosis with early cancerous changes: *a*, the swelling and hydrops of the proliferated basal cells; *b*, the segregation and invasion of the submucosa; *c*, intraepithelial growth, and *d*, a mild lymphocytic infiltration.

what seem to be small droplets similar to those seen in embryonic fat cells or foam cells. The nuclei are usually larger than those of normal basal cells, the chromatin may be more rarefied and the nucleolus is often rather large.

In some places these altered basal cells proliferate to form a layer only two or three cells thick, while in other places they segregate into clumps or nests which invade the submucosa (fig. 2 *b*). These nests may also invade the overlying mucosa (intraepithelial growth), where they stand out in sharp contrast to the normal mucosal cells because

of their clear hydropic protoplasm and a clear cleft or space around them (fig. 2, *c*). Individual heavily pigmented cells or lightly pigmented cells with clear protoplasm may be seen in the superficial layers of the mucosa, sharply demarcated from their surroundings. At some sites the altered basal cells invade and entirely replace the overlying mucosa. Occasionally small epithelial whorls with slight cyst formation may be seen beneath the mucosa. In the submucosa there are also varying numbers of cells containing phagocytosed pigment which has migrated from the basal cells. Sometimes areas containing a considerable number of pigment-bearing phagocytes are noted beneath a relatively normal-appearing nonpigmented mucosa, beneath a thin atrophic mucosa or at a site with little or no mucosa on the surface. Such areas apparently represent a regression of the lesion with resultant disappearance of the mucosa, which in places has not regenerated or has regenerated with normal or atrophic epithelium, leaving only the phagocytosed pigment in the submucosa as remains of the active process. There is frequently a chronic inflammatory reaction of plasma cells and other types of lymphocytes, principally at the limit of the extension into the submucosa (fig. 2, *d*, and figs. 3 and 4). As the characteristic diffuseness of the lesion would indicate, these precancerous changes may occur over wide areas throughout the basal layer (fig. 3). As the lesion becomes malignant it may remain diffuse, with little localized thickenings, elevations or tumor formations (fig. 4); the individual cells are characteristically polygonal and are clearly demarcated by their protoplasmic borders.

ANALYSIS OF SEVENTEEN CASES

A series of 17 cases [1] of precancerous and cancerous melanosis of the conjunctiva, including the 8 cases previously reported,[2] have been studied. On the basis of biopsy evidence, in 5 of the 17 the disease was considered to be in the precancerous stage. In 4 of these the patient was treated effectively by irradiation with 250 to 550 millicurie minutes of radon in a glass bulb two to five times with no filter in contact with the lesion. The melanosis disappeared and has not recurred to date after eight years, seven years, six years and one year, respectively. Two of the patients were treated surgically as well as by irradiation, because of the diffuseness of the lesions, and in 2 there were manifestations elsewhere in the conjunctiva which required additional irradiation. In view of the radiosensitivity of ectodermal tissue in general, it is not surprising that this lesion, arising as it does from the epithelium, should be radiosensitive. It may also show spontaneous regression. In the only case in this series in which such regression occurred (fig. 5 *A*, *B* and *C*), however, there has recently been a recurrence of the pigmentation over the former site. Areas of regression occurring along with

2. Reese, A. B.: Precancerous Melanosis and Diffuse Malignant Melanoma of the Conjunctiva, Arch. Ophth. **19**:354-365 (March) 1938.

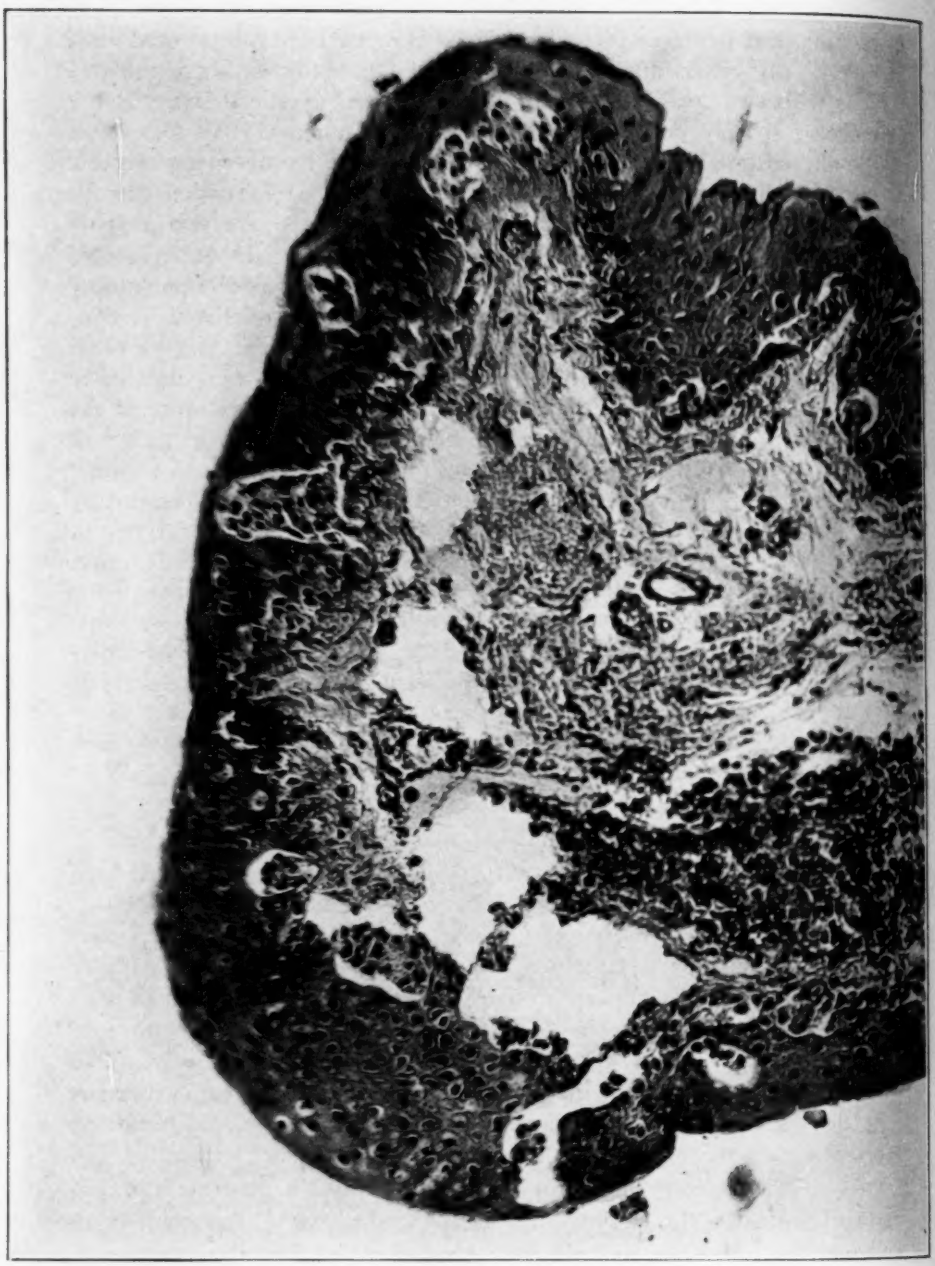

Fig. 3.—A section of tissue removed for biopsy in a case of precancerous melanosis with early cancerous changes. The diffuse nature of the lesion is shown by the activity of the basal layer over the entire specimen, as evidenced by proliferation, intraepithelial growth and tendency to spread into the submucosa, especially at one large site, where there is also some lymphocytic infiltration.

Fig. 4.—A section of tissue removed for biopsy in a case of well advanced cancerous melanosis. The surface epithelium has been completely replaced by cancer, which also shows extension into the submucosa. There is some lymphocytic infiltration at the deeper limits of the extension.

areas of progression have been reported in cases of precancerous melanosis of the skin; there have even been authentic cases in which the regression has continued to the point of complete and permanent disappearance of the lesion.

In 12 of the 17 cases the melanosis was considered to be in the malignant stage. Seven of the patients are dead, 1 is presumably dead but has been lost track of and 4 are living. Of these 4, 1 refused to have an exenteration of the orbit (fig. 1), 1 had an exenteration one year before the time of writing and 1 had an exenteration three months before. Only 1 patient was living and well an appreciable period (nine years) after exenteration. The last mentioned is the only patient in the series known to have been treated properly, the exenterations for the other 2 having been performed too recently to be judged. It is clear that exenteration should be performed early, but the rather unimportant clinical appearance of the lesion, particularly in its early stages, and the fact that its diffuseness is not appreciated, lead too often to the employment of such halfway measures as repeated local excisions and sometimes irradiation. These temporizing procedures entail a loss of time which may have fatal consequences. There is no contraindication to biopsy. Characteristically, the conjunctiva is widely involved (fig. 3), even over areas not appreciable clinically except by study with high magnification. As the disease is one which ultimately, and at times almost simultaneously, affects the conjunctiva over wide areas or in its entirety, the removal of all of the conjunctiva is usually indicated. If the adjacent skin of the lids is involved this too should be widely excised.

DIFFERENTIAL DIAGNOSIS

Precancerous melanosis may be confused with the following conditions:

1. *Congenital Melanosis of the Conjunctiva.*—This is a localized area of pigmentation, usually adjacent to the limbus, in an otherwise normal-appearing conjunctiva; it is present from birth or shortly thereafter, undergoes no change throughout life and is due to pigment in the basal layer of an otherwise normal conjunctiva (fig. 5 *D*). The pigment is black, in contrast to the yellowish appearance of precancerous melanosis. The basal layer of the conjunctiva adjacent to the limbus is a potentially pigment-bearing tissue, and in highly pigmented persons and races this melanosis in a diffuse form is seen normally.

2. *Melanosis Oculi.*—This is an increase in the pigmentation of all the potentially pigment-bearing tissue in and around one eye as compared with the fellow eye. If the conjunctival aspect is particularly pronounced (fig. 5 *E*) it may be confused with precancerous melanosis, but the dense pigmentation of the entire uveal tract of the involved eye as compared with that of the fellow eye serves to distinguish the two conditions.

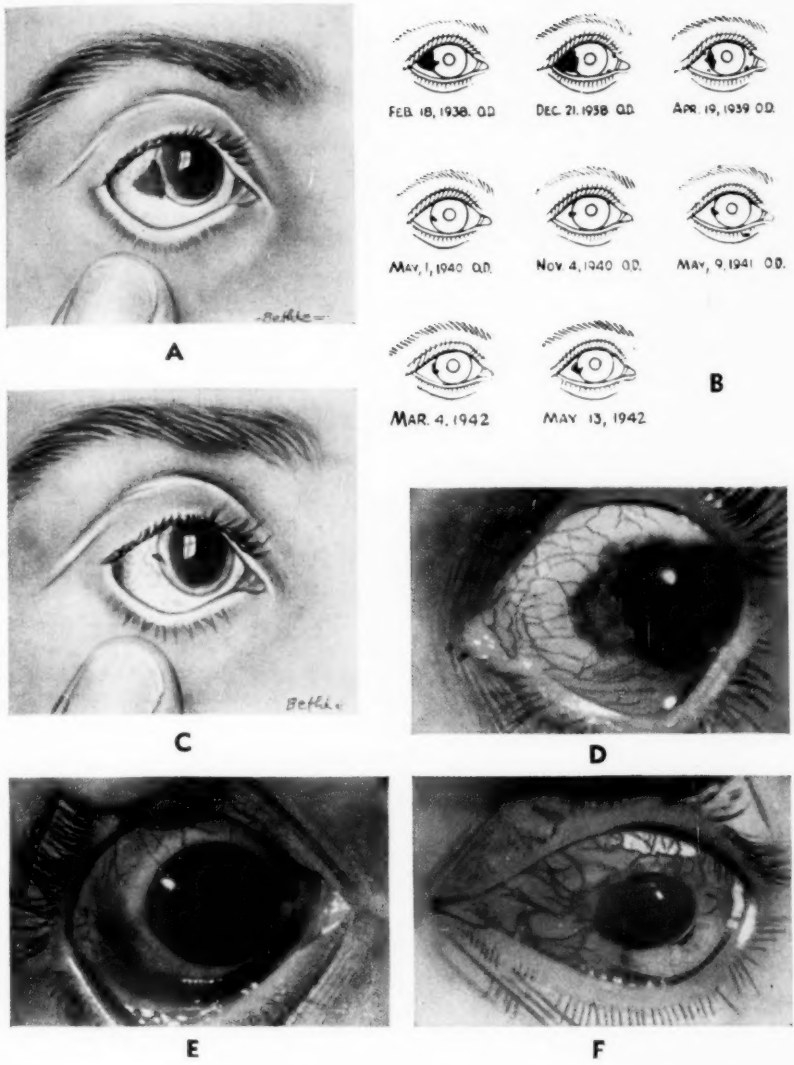

Fig. 5.—A woman aged 55 noticed what she thought was a hemorrhage the size of a pinhead on the white part of the right eye in 1931. This gradually enlarged. She was observed first in February 1938, at which time there was a nonelevated pigmented lesion of the bulbar conjunctiva temporally adjacent to the limbus, measuring 5 by 5 mm. and encroaching for 1 mm. on the cornea (*A*). There was a diffuse fine granular pigmentation of the bulbar conjunctiva nasally. The patient was observed elsewhere from time to time until December 1938, when it was noted that the lesion measured 7 by 7 mm., with no apparent increase in the granular pigmentation nasally. In April 1939 it was observed that the lesion had regressed. The regression occurred spontaneously, as there had been no treatment. *B* shows consecutive sketches drawn to scale. There was some reappearance

Legend Continued on Reverse Side

of the pigment at the last observation in May 1942, and later observations showed further progression. *C* shows the appearance in May 1940, at the height of the spontaneous regression. The fine granular pigmentation of the bulbar conjunctiva nasally also disappeared. In May 1941 no actual recurrence was seen, but there was noted with the slit lamp a fine granular pigmentation at the site of the former lesion and for some distance around it. In May 1942 a slight increase in the size of the lesion was recorded (from 1 to 2 mm. and a 0.5 mm. projection on the cornea to 1 by 3 mm. and a 1 mm. projection on the cornea). Also, slight diffuse pigmentation of the bulbar conjunctiva nasally was again noted.

In addition to the ocular findings, there were pigmented lesions elsewhere which were undergoing changes. In April 1939 a pigmented lesion on the right cheek of unknown duration disappeared spontaneously, leaving a slightly elevated nonpigmented area, with an uneven surface, measuring 5 by 3 mm. In May 1941 there was a slightly brownish papule in the right periauricular region, measuring 4 mm. in diameter, of three months' duration. In October 1941 this lesion had disappeared.

D, congenital melanosis of the conjunctiva.

E, melanosis oculi with especially severe involvement of the conjunctiva.

F, eye of a woman aged 46 who noted in March 1937, after a streptococcic infection of the throat, that there was an elevated brownish area over the inner aspect of the right eyeball. She thought this regressed somewhat during the following several months. After a year, however, it had enlarged so that at an examination made elsewhere in May 1938 it was seen to be elevated and measured 9 by 5 mm. It was excised with a wire snare, and a report of nonpigmented melanoma was made. The specimen could not be obtained for examination. There was a recurrence at the site of the former lesion. I saw the patient for the first time in October 1938. There was an elevated, almost pedunculated red mass 5 mm. in diameter at the limbus of the right eye between 1 and 2 o'clock. There was also a slightly elevated and pigmented lesion of the bulbar conjunctiva of the left eye at about 3 o'clock measuring 5 by 3.5 mm. A biopsy was made of the lesion on the right eye, and this showed malignant melanoma. The patient refused an exenteration until March 1939. At this time the mass measured 7.5 mm. in diameter, extended from 12 to 3 o'clock and encroached on the cornea. At the time of the exenteration the small lesion on the bulbar conjunctiva of the left eye was excised. This proved to be a nevus.

3. *Nevus.*—The typical nevus is not to be confused with precancerous melanosis. Sometimes, however, a nevus is flat, diffuse and irregularly pigmented. It may then to some degree resemble an area of precancerous melanosis, but the fact that the nevus has been present since earliest recollection and that it is always to some extent elevated, with a rather undulating and irregular surface, should differentiate it. A biopsy would establish the diagnosis decisively.

Sometimes a patient gives a history of a nevus first noticed late in life or a history of a congenital nevus which has shown signs of growth. This apparent acquisition of, or increase in growth of, a nevus seems to be due in most instances not to actual growth but to an increase in the pigment content of a preexisting nevus, which, on the one hand, was formerly nonpigmented or, on the other hand, was formerly only partially pigmented. The change in pigment content is due merely to the transition of the premelanin in the nevus cells to melanin, a process induced by oxidation.

I have never seen malignant melanoma of the conjunctiva or skin which could be said with certanity to have arisen from a congenital nevus. In 4 cases, however, the melanoma was suspected of having arisen from a nevus, not because of any known preexisting nevus, but because of clinical and histologic evidence. In 1 of the 4 there was a nevus of the bulbar conjunctiva of the fellow eye, which was verified microscopically (fig. 6) and provided an additional presumptive indication of the origin of the melanoma. Clinically, the malignant melanoma in these cases comprised well localized, even pedunculated, single or multiple tumor masses (fig. 5*F* and fig. 6); histologically these were composed of more spindle-shaped syncytially arranged cells which had no relation to the basal epithelium and in general resembled those of melanoma occurring in the uveal tract (fig. 6) In the malignant phase the anaplasia of the cells frequently makes differentiation between a melanoma arising from melanosis and one arising from a nevus impossible (figs. 4 and 6).

A review of the voluminous literature on the subject revealed 42 cases[3] that could be identified as definitely or presumably cases of

3. Blanch, A.: Mélano-sarcome de la paupière, Rec. d'opht. **4**:620, 1882. Boulai: Bènignitè relative des carcinomes mélaniques superficiels du globe oculaire (3 observations), Clin. opht. **20**:155-162, 1914. Capdeville, P. J.: Contribution à l'étude de la mélanose conjonctivale, Thesis, Bordeaux, no. 111, A. Destout Ainé & Cie, 1911, p. 50. Cappez, H.: Nature et mode de formation des taches mélaniques conjonctivales accompagnant les tumeurs mélaniques de la conjonctive, Arch. d'opht. **27**:67-76, 1907. Capron, F. P.: Multiple Melanotic Nevi of Conjunctiva, with Malignant Invasion of the Corneal Limbus, Tr. Am. Ophth. Soc. **14**:322-326, 1915. Cashell, G. T. W.: Malignant Change in Case of Melanosis, Proc. Roy. Soc. Med. **33**:545-549, 1940. Castroviejo, R.: Epibulbar Nevocarcinoma with Almost Total Corneal Involvement, Am. J. Ophth. **14**:757-768, 1931. Collins, E. T.: Discussion

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melanoma which arose from acquired precancerous melanosis. Only 2 cases could be found which could be identified definitely as cases of melanoma which arose from a preexisting nevus. One of these was reported by Lane [4] and the other by Rosenstein.[5] In the latter case active growth followed Koch-Weeks bacillus conjunctivitis. There was

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on Intra- and Extra-Ocular Melanomata, Tr. Ophth. Soc. U. Kingdom **46**:86-136, 1926. Corsi, H.: Mélanose Circonscrite Précanceureuse: Three Cases, Proc. Roy. Soc. Med. **32**:261-263, 1939. Chevallereau, A.; Offret, M. A., and Boussi, P.: Tumeurs épibulbaires, Bull. et mém. Soc. franç. d'opht. **31**:529-534, 1914. Cunningham, J. F.: Melanosis of Right Eyeball, Proc. Roy. Soc. Med. **22**:1015, 1929. Dor: Pigmentation mélanique de la conjonctive, Mém. et compt. rend. Soc. d. sc. méd. de Lyon (1878) **18**:61, 1879; Une malade atteinte de pigmentation mélanique de la conjonctiva et d'une partie de la cornée, Lyon méd. **28**:101, 1878. Fano: Mélanose et tumeur mélanique de la conjonctive, Gaz. d. hôp. **45**:651, 1872; Recidive d'une tumeur mélanique de la conjunctiva après une première extirpation, ibid. **46**:156, 1873. Fromaget, C.: Mélanose conjonctivale et lentigo malin, J. de méd. de Bordeaux **30**:261, 1900. Ibrahim, F. G.: Melanotic Sarcoma of the Conjunctiva, Bull. Ophth. Soc. Egypt **30**:143-144, 1937. Löhlein, W.: Ueber Melanosis der Bindehaut, Klin. Monatsbl. f. Augenh. **68**:389, 1922. McKee, J. W.: Melanosarcoma at the Limbus, Am. J. Ophth. **13**:407-408, 1930. Moore, R. F.: A Conjunctival Pigmented Mole of Rapid Growth, Tr. Ophth. Soc. U. Kingdom **35**:226, 1915. Morton, H. M.: Atypically Situated Sarcoma of the Conjunctiva, J. A. M. A. **95**:1804-1806 (Dec. 13) 1930. Posey, W. C.: Report of a Case of Melanosarcoma of the Palpebral Conjunctiva Illustrating the Malignancy of Such Growths, Arch. Ophth. **55**:131-135, 1926. Roper, A. C.: Melanotic Sarcoma of the Conjunctiva with Pigmented and Non-Sarcomatous Growths in Skin, Tr. Ophth. Soc. U. Kingdom **32**:117-118, 1912. Rugg-Gunn, A.: Two Cases of Malignant Melanomata (Multiple) of the Conjunctiva and Eyelids, Proc. Roy. Soc. Med. **27**:353, 1934. Schmidt, R.: Isolierte Melanosis corneae. 8 Jahre nach Exzision eines oberflächlichen Melanosarkoms am Hornhautlimbus, Klin. Monatsbl. f. Augenh. **93**:164-170, 1934. Silex, P.: Ueber epibulbäre melanotische Sarcome, Arch. f. Augenh. **20**:59-69, 1889. Snell, A. C.: An Epibulbar Melanosarcoma of the Limbus Which Completely Disappeared Under X-Ray Treatments, Tr. Am. Ophth. Soc. **14**:556-560, 1916. Walker, C.: Melanosis of Lid and Conjunctiva, Proc. Roy. Soc. Med. **21**:689-690, 1928. Weisman-Netter, and Blum, J.: Sur un cas de naevo-carcinoma conjonctivale, Bull. Soc. d'opht. de Paris, 1908, pp. 253-255. Weber, H.: Multiple Melanosarkome der conjunctiva bulbi, Klin. Monatsbl. f. Augenh. **88**:703, 1932. Wilder, W. H.: Melanotic Epibulbar Tumor Dispelled by the Use of Radium, Arch. Ophth. **53**:355-361, 1924. Wischhusen, A. G.: Ein polypenartiges Melanosarkom der Conjunktiva, Klin. Monatsbl. f. Augenh. **65**: 923, 1920. Zeidler, M.: Melanosis conjunctivae, ibid. **82**:521-522, 1929. Dallos, J.: Bösartig entartete Bindehautmelanose, ibid. **91**:678, 1933. Hutchinson, J.: On Tissue-Dotage, Arch. Surg., London **3**:315, 1891. Lafon, C., and Teulières, T.: Tumeur mélanique primitive de la paupière, J. de méd. de Bordeaux **38**:536, 1908.

4. Lane, F.: Extensive Sarcoma Originating from a Pigmented Naevus of the Conjunctiva, Am. J. Ophth. **8**:698-699, 1925.

5. Rosenstein, A. M.: Rasches Wachstum eines Limbus-Sarkoms in einem vererbten Naevus in Anschluss an eine Konch-Week Konjunktivitis, Klin. Monatsbl. f. Augenh. **75**:679-681, 1925.

also a case reported by von Berger,[6] in which he assumed that melanoma arose from a nevus after an injury because the fellow eye had a pigmented nevus at the limbus. In 9 cases[7] there was apparently no lesion prior to the onset of malignant changes, and these cases may

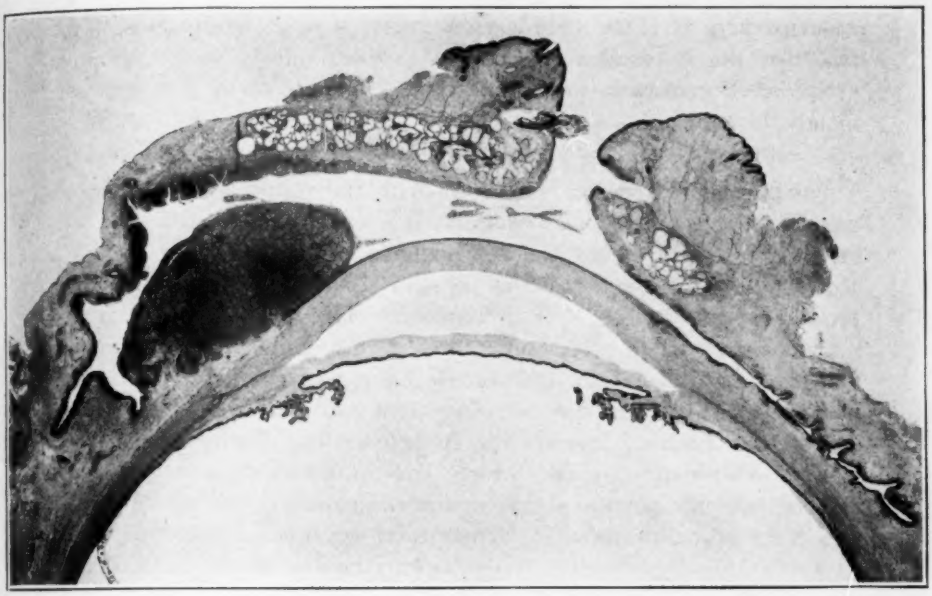

Fig. 6.—Microscopic section of the eye pictured in figure 5*F*, showing an encapsulated tumor occupying the nasal limbus and encroaching somewhat on the cornea. The tumor is composed of highly anaplastic cells, which vary greatly in size and shape, with numerous mitotic figures and some multinucleated cells. In the less rapidly growing areas the cells are spindle shaped, with delicate chromatin marking and large nucleoli. An occasional cell contains some pigment. The diagnosis was malignant melanoma. The assumption was that the tumor arose from a nevus. This was based on clinical and histologic characteristics, which were different from those of malignant melanoma (cancerous melanosis) arising from precancerous melanosis. Also, there was a proved nevus of the bulbar conjunctiva of the fellow eye. In January 1940 a preauricular gland was palpable on the right side. By February the lesion had disappeared. In July there was a recurrence of the palpable node, which now measured 2 cm. in diameter. It was excised and showed metastatic malignant melanoma. In March 1942 there was no evidence of disease and the patient was in good health.

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6. von Berger, F.: Sarcoma alveolare a cellule rotonde della cornea, Ann. di ottal. e clin. ocul. **6**:401-410, 1922.

7. Albrich, K.: Epibulbäres Sarkom mit pigmentierung des Hornhautepithels, Klin. Monatsbl. f. Augenh. **71**:476-480, 1923. Ball, J. M., and Lamb, H. D.: A Case of Epibulbar Melanotic Sarcoma Occurring Sixteen Years After Injury, Arch. Ophth. **52**:80-83, 1923. Chance, B.: Recurrent Sarcomata at the Limbus, Tr. Am. Ophth. Soc. **14**:550-556, 1916. Crigler, L. W.: Epibulbar Sarcoma with

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be instances of melanosis malignant from the beginning. Many reports in the literature had to be discarded as unclassifiable because of incomplete data.

In my experience cancerous melanosis is much more frequent than malignant melanoma arising from a nevus. The ratio of the cases reported here is 17 to 4, or approximately 4 to 1, irrespective of the fact that the 4 cases were grouped as such mostly on presumptive grounds. For cases in the literature the ratio was 41 to 3, or approximately 14 to 1.

CONCLUSIONS

Acquired precancerous melanosis with the resulting diffuse malignant melanoma (cancerous melanosis) is a lesion different from the congenital neurogenic nevus and the malignant melanoma that may be a sequel to it. The occurrence of pigment seems to be the only characteristic the two lesions have in common. The first is acquired about middle age or later; affects in a very diffuse manner the conjunctiva and/or the adjacent skin, with no elevation (except in the late malignant stage, when there may be some slight localized tumor formation); arises from the basal layer of the epithelium; has distinguishing histologic characteristics in the benign and in the malignant phase; is inevitably a precancerous lesion in the earlier stage, and is radiosensitive in the precancerous stage. The second lesion is congenital or makes its appearance shortly after birth, appears as a localized elevated pigmentation, rarely becomes malignant but if it does manifests itself as a localized tumor mass, is probably of neurogenic origin in the benign phase, is composed of characteristic nevus cells, which seem to have no relation to the basal layer of the epithelium, in the malignant phase has distinguishing histologic characteristics, in the benign phase is not inevitably precancerous and is completely radioresistant.

As the malignant melanoma arising from acquired melanosis is a different tumor from the malignant melanoma arising from a nevus, it seems advisable to designate the two differently to avoid the necessity of always stating which type is meant. The term "cancerous melanosis" seems to be suitable to designate the type of malignant melanoma arising from acquired precancerous melanosis.

Miss Lilly Kneiske assisted in this study.

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Microscopic and Macroscopic Sections, Arch. Ophth. **44**:41-48, 1915. Van Duyse, D.: Naevosarcinome de la cornée, Arch. d'opht. **40**:705-728, 1923. Fernando, A. S.: Report of a Case of Melanosarcoma of the Conjunctiva, Arch. Ophth. **52**:168-169, 1923. Goulding, H. B.: A Case of Exenteration for Pigmented Sarcoma Growing from the Limbus, Tr. Ophth. Soc. U. Kingdom **44**:432, 1924. Luedde, W. H.: Recurrent Pigmented Growth at Limbus, Tr. Am. Ophth. Soc. **21**:107-118, 1923. Veil, P.: Étude anatomo-clinique d'un cas de naevo-cancer du Limbe scléro-cornéen et de ses métastases, Arch. d'opht. **45**:506-514, 1928.

WEATHER AND OCULAR PATHOPHYSIOLOGY

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In a series of papers that have been published in recent years Duggan [1] has projected a conception of ocular pathology predicated on vascular dysfunction. It is based both on physiologic and on clinical observation, and its validity has apparently been established by successful therapeutic practice. Primarily Duggan stressed the pathologic significance of vascular spasm, both in precipitating the clinical episode and in initiating the primary dysfunction. Such spasm, transient or prolonged, localized or occurring as part of a more general increase in vascular tone, brings in its train a series of local disturbances in water balance, in cellular permeability, in ion balance (p_H, potassium/calcium, chlorides, phosphates), etc., with resulting clinical phenomena that may take various forms.

Duggan has called attention to the precipitation of the acute episode with chilling or with change in the weather, though obviously other factors may be effective in the vascular balance, for example allergic, traumatic and toxic influences. In view of the fact that every one is conditioned by weather, some persons to a greater degree than others, and also by season, and that environmental variability is reflected both in stimulation and in fatigue in the mechanisms of vascular (autonomic) adjustment, I thought it might be of interest to relate some of the clinical events described by Duggan to the meteorologic situation of the time. To this end a series of small meteorograms was prepared for each of the case histories.

Because of the extent of the material available it is not feasible to include each case; a few histories have been selected and quoted from the separate studies. The relations illustrated are, however, characteristic.

UVEAL DISEASE

CASE 1 (Case 1[1a]).—*Acute Iritis, Recurrent.*—M. Z., a man of 28, had acute iritis of the left eye in July 1935, while being treated for gonorrheal urethritis. Treatment was started on the fourth day, and thirty-five days of treatment was

1. Duggan, W. F.: (*a*) Vascular Basis of Uveal Disease: Acute Anoxia as Fundamental Pathologic Physiology, Arch. Ophth. **24**:1123 (Dec.) 1940; (*b*) Role of Anoxia in the Production of Episcleritis and Scleritis: Treatment with Vasodilators, ibid. **25**:113 (Jan.) 1941; (*c*) Acute Exudative Choroiditis: Pathologic Physiology; Treatment with Vasodilators, ibid. **23**:930 (May) 1940; (*d*) Use of Vasodilators in Treatment of Retrobulbar Neuritis, ibid. **16**:380 (Sept.) 1936.

required for cure. On March 4, 1937 [*1*, chart 1], he had an attack in the right eye, which became worse after injections of gonococcus vaccine. Seventy-three days of treatment were necessary for cure this time.

On Feb. 11, 1938, he was seen with a fresh attack in the right eye [*2*, chart 1]. There was a synechia nasally, with marked circumcorneal injection and tearing. Treatment consisted of the instillation of atropine, the application of hot compresses and the administration of salicylates. On March 2 the condition was worse [*3*, chart 1], and the eye was very soft. The patient was then ordered to use 30 mg. of erythrityl tetranitrate twice daily by mouth for one week. He felt better on March 3. On March 4 the eye was definitely whiter, and there was no tenderness or pain. On March 9 the vision was 20/30, and the eye was practically white. On March 18 [*4*, chart 1] there was a recurrence of circumcorneal injection; so he was given 0.1 Gm. of sodium nitrite intravenously; one hour later the

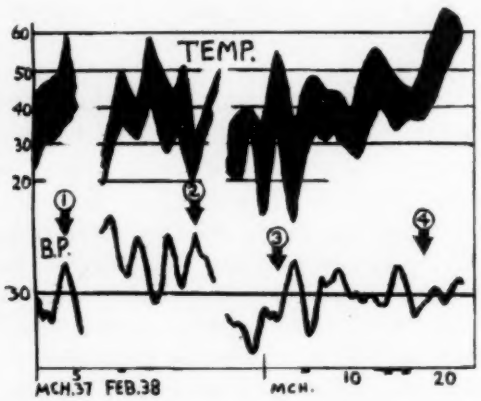

Chart 1.—Meteorogram to illustrate the four clinical episodes in case 1. The daily maximal and minimal temperatures are indicated in the black field and the barometric pressure in the tracing below. Precipitation is indicated by the black bars beneath the date line. The numbered arrows indicate the day of the clinical episodes.

eye was whiter. The injection was repeated on March 20. The patient was last seen on March 23, when the eye was still quiet.

One notes the acute episode of March 4, 1937 (*1*), occurring at a sharp barometric crest after low environmental temperatures of the preceding days. The attack (*2*) on Feb. 11, 1938 occurred during a similar barometric situation, and the accentuation of illness (*3*) became evident at a time when the barometric pressure had increased from the low of February 27, reaching a crest on March 4; the temperature had been low on March 1. Finally, accentuation (*4*) occurred with the passage of a colder air mass, beginning on March 14.

REACTIONS TO WEATHER

One is apt to take change in the weather for granted, but such change involves a fundamental difference in the air mass in which human beings exist.

Polar air is diametrically opposite to tropical air in its character and in its demands on the human organism. The former is heavy, cold, clear and dry. The organism seeks to shut itself off from the unfavorable effect of the cold by a sympathicotonic phase, with increased arteriolar tone, with sugar mobilization, with relative alkalinity, etc. Tissues, especially peripheral tissues, become relatively anoxic (stasis anoxia).

The tissue status is reversed when the metabolic products of anoxia begin to enter the circulation; the organism is then stimulated. The phase of stimulation may proceed to fatigue, with a reversal of the tissue status, and with this reversal the p_H is lowered, permeability is increased, the blood pressure falls and hydration is accentuated.

Obviously any tissue focus that cannot adjust rapidly and adequately to such change begins to reflect local symptoms; swelling may cause pain, there may be hyperemia, an exudate may increase or tissues may undergo more rapid autolysis.

Tropical air is warm, moist and lighter in weight, and its effects, unless excessive temperatures are reached, are opposite to those of polar air. The passage of the tropical air mass, however, synchronized with the after-effect of a polar air mass, may augment the stage of stimulation or of fatigue and result in unusually low blood pressure, in excessive hydration, in low p_H and in pronounced augmentation of digestive phenomena.

In the midst of the belt of circumpolar circulation, a study of the metabolism of the normal as well as of the sick person reveals a corresponding pendulation of the organic status, and with this pendulation clinical episodes of the type here discussed actually mirror the changing physiologic status of the organism as it is pushed to and fro by the environmental change.[2]

CASE 2 (case 2[1a]).—*Acute Iritis.*—F. T., a man of 60, had acute iritis of the right eye which was clinically cured in eleven days with routine therapy. There were permanent synechiae. The Wassermann reaction of the blood was negative. Forty years earlier the patient had had gonorrhea.

On June 3, 1938, he was seen with a fresh attack of iritis in the left eye [*1*, chart 2]; scopolamine and salicylates were ordered. On June 9 the condition was much worse [*2*, chart 2]; the pupil was small, and there were marked circumcorneal injection and pain and a fibrinous exudate in the anterior chamber.

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2. Petersen, W. F.: Weather and Biochemical Variability, Arch. Biochem. **1**:269 (Dec.) 1942.

In the meteorogram one observes that the attack occurred immediately in the wake of a barometric crest and the passage of a cold air mass (*1*). The patient became worse (*2*) with the passage of the next polar episode.

This patient was worse on June 9, and Dr. Duggan's fourth patient had the onset of his attack June 10 (*1*). Obviously the same environmental situation that had made the second patient worse precipitated the attack in the fourth patient.

CASE 3 (case 3[1a]).—*Acute Iridocyclitis Following Removal of Tooth.*—H. H., a man of 28, was seen on April 29, 1938 [*3*, chart 3], with acute iridocyclitis of the right eye of seven days' duration [*2*, chart 3]. It began one to two days after extraction of the upper right first molar tooth [*1*, chart 3].

The vision was 20/70; this corrected to 20/30— with concave lenses. In addition to marked circumcorneal congestion, the iris was swollen, dilated venules

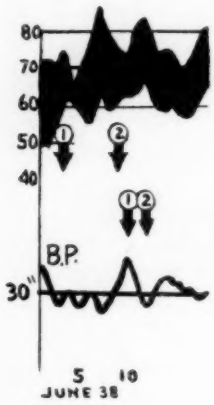

Figure 2

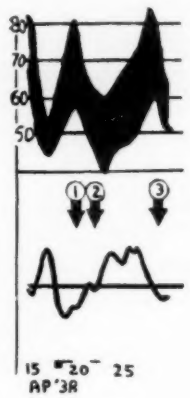

Figure 3

Chart 2.—Meteorogram to illustrate the clinical events in cases 2 and 4.

Chart 3.—Meteorogram to illustrate the clinical events in case 3.

were visible on its anterior surface, the anterior chamber was full of cells and the disk was seen indistinctly. There was a synechia nasally. The patient was given 1 drop of scopolamine daily and five daily intravenous injections of sodium nitrite.

In this instance the clinical episode (*2*) occurred with the passage of a major polar air mass. Of particular interest is the association with the extraction of a tooth, and the situation reveals the underlying unity of the mechanism at play. An anoxic phase will result in swelling about an infected tooth, and, because of the unyielding alveolar structure, such swelling results in aggravation of symptoms. In this instance the barometric crest was reached on April 17. With this change in the weather an anoxia became effective; the patient had his tooth extracted three or four days later when the symptoms became unusually severe (*1*).

But with such extraction bacteria flood the blood stream, and if any areas of tissue are present where anoxia has existed, foci of dysfunction, with adhesive capillary walls, will be present, and some bacteria may localize and cause an acute inflammatory reaction.[2a]

It is possible that in case 3 there was such an episode. Milliken and I[3] have demonstrated the process at length, and Nedzel[4] has provided the experimental background as it is evident in endocarditis.

CASE 4 (case 6[1a]).—*Chronic Iridocyclitis.*—F. M., a woman of 25, was seen on Oct. 3, 1938 [*3*, chart 4] because of blurred vision in the right eye and redness of both eyes for three weeks [*1*, chart 4]. She had had recurrent attacks of iridocyclitis in both eyes for several years. She had been using atropine and hot compresses for one week [*2*, chart 4].

The vision of the right eye was 20/30—. There were slight circumcorneal congestion and many posterior corneal deposits, the iris markings were blurred and the vitreous was hazy.

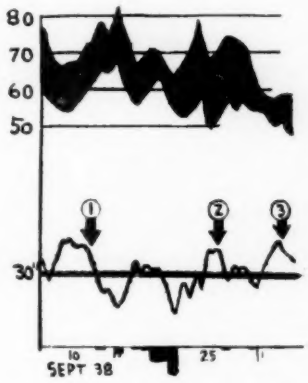

Chart 4.—Meteorogram to illustrate the clinical events in case 4.

The vision of the left eye was reduced to perception of hand movements. This eye showed, in addition to the changes noted in the right eye, a complicated cataract, a postoperative coloboma of the iris and many posterior synechiae.

The patient continued to use atropine and hot compresses and was given six daily intravenous injections of sodium nitrite (0.1 Gm.) followed by 15 mg. of erythrityl tetranitrate by mouth twice daily for two weeks.

Again the weather situation reveals the cause of the changing clinical picture. The onset three weeks before the patient was seen by the physician corresponded to the passage of a major polar air mass (*1*);

2a. Burrows, H.: Some Factors in the Localization of Disease in the Body, London, Baillière, Tindall & Cox, 1932.

3. Petersen, W. F., and Milliken, M. E.: Cardio-Vascular-Renal Disease, in The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, Inc., 1937, vol. 4, pt. 1, chap. 7, p. 545.

4. Nedzel, A. J.: Experimental Endocarditis, Arch. Path. **24**:143 (Aug.) 1937.

accentuation one week before he was seen (*2*) occurred with a later barometric crest, and, finally, the patient went to the ophthalmologist for relief (*3*) at the next barometric crest.

ROLE OF ANOXIA IN THE PRODUCTION OF EPISCLERITIS AND SCLERITIS

I shall turn next to patients with episcleritis and scleritis, the case records being quoted from a paper of Duggan's.[1b]

CASE 5 (case 1,[1b] episcleritis).—W. P., a man of 58, was seen on March 24, 1938 [*2*, chart 5] with the complaint that on March 18 the right eye had become red and teared. Chemosis and photophobia developed on March 24. The patient had had malaria, typhoid fever and yellow fever. His upper teeth were false, and he had several rotten roots and one capped tooth in his lower jaw. There was no

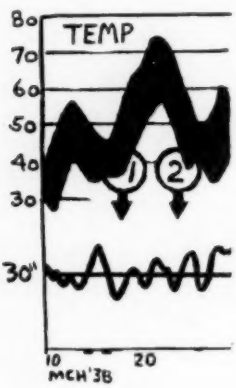

Figure 5

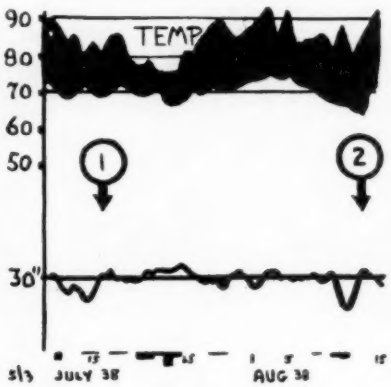

Figure 6

Chart 5.—Meteorogram to illustrate the clinical events in case 5.
Chart 6.—Meteorogram to illustrate the clinical events in case 6.

history of gonorrhea, syphilis or tuberculosis, and his general physical condition was otherwise good.

It will be noted that the onset in this instance followed the passage of a major polar air mass with its barometric crest on March 15. Precipitation had been continuous from March 12 to 18, and with the passage of the next polar air mass, on March 18, the eye became red and teared. Accentuation followed with a decline of temperature after the tropical crest on March 23.

CASE 6 (case 2,[1b] episcleritis).—W. W., a man of 30, was seen on Aug. 13, 1938 [*2*, chart 6], with the complaint that the right eye had been red, painful and sensitive to light for one month [*1*, chart 6]. He gave a history of many previous attacks of episcleral inflammation in both eyes for several years.

Vision in the right eye was 20/30. There was a typical nodule of episcleritis temporal to the limbus, with several old corneal opacities in the temporal half of the cornea.

Again one observes the usual interrelation: onset with a barometric crest after a phase of low pressure, accentuation and, finally, medical attention (*2*), with a similar episode a month later.

CASE 7 (case 3,[1b] episcleritis).—M. M., a man of 61, was seen on Sept. 23, 1938 [*2*, chart 7], with the complaint that the right eye had been red and painful for four days [*1*, chart 7]. . . . The patient returned on September 30 [*3*, chart 7] with the complaint of inability to sleep at night because of pain in the eye.

The onset of the symptoms occurred with a barometric crest (*1*) and a marked period of precipitation, the patient went to the physician (*2*) when there was passage of a subsequent polar air mass and, finally (*3*) the increase in the amount of pain was apparently associated with the passage of a barometric crest shortly before the patient's admission

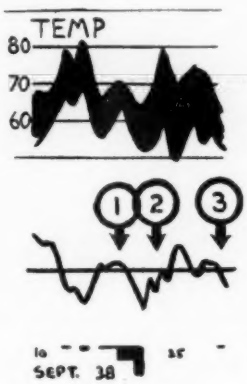

Figure 7

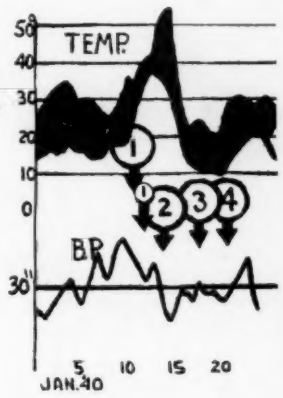

Figure 8

Chart 7.—Meteorogram to illustrate the clinical events in case 7.
Chart 8.—Meteorogram to illustrate the clinical events in case 8.

to the hospital. The period is one already observed in case 4 (case 6 of Duggan's previous series).

CASE 8 (case 4,[1b] brawny scleritis).—Mrs. C. H., 68 years of age, was seen on Jan. 14, 1940 [*3*, chart 8], with the complaint that the right lids had been swollen and the right eye had been fiery red, tender, painful and tearing since awakening on January 12 [*2*, chart 8]. She also had a severe headache. A similar condition had developed in the left eye on January 13. The only apparent cause that could be elicited was that she had been out in the cold on January 11 and 12 [*1*, chart 8]. Several years previously she had suffered from a severe attack of rheumatism, and she still had occasional attacks of pain and tenderness in her knees.

The vision was 20/30— in the right eye and 20/20— in the left eye. The right eye showed marked chemosis and a purplish red congestion of the episcleral

vessels from the limbus to the equator. The eyeball was extremely tender, especially near the insertions of the rectus muscles. There was also slight edema of the lids. The left eye showed the same changes to a slightly lesser degree.

The pupils reacted normally, and the tension, fields and fundi were normal. Incipient lens opacities were present, more marked in the right than in the left eye.

She was immediately given 0.1 Gm. of sodium nitrite intravenously and told to take 15 mg. of erythrityl tetranitrate that night.

When she returned, on January 18 [*4*, chart 8], she was markedly improved. The edema of the lids, chemosis, pain and tenderness were no longer present, and all of the episcleral injection had disappeared except a tiny patch nasal and temporal to each limbus. A second injection of sodium nitrite was given at this time.

On January 22 the eyes were completely white and showed no signs or symptoms of the scleritis.

The initiation of the episode followed in the wake of the great barometric crest evident in the meteorogram.

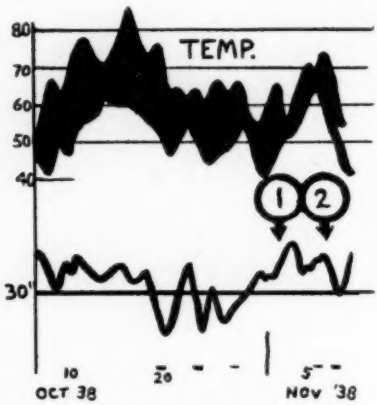

Figure 9

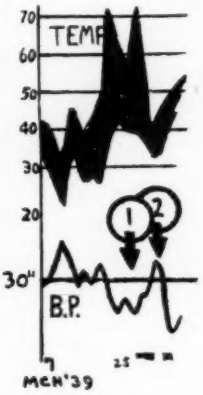

Figure 10

Chart 9.—Meteorogram to illustrate the clinical events in case 9.

Chart 10.—Meteorogram to illustrate the clinical events in case 10.

ACUTE EXUDATIVE CHOROIDITIS

A characteristic picture is presented in case 9, a report of which follows:

CASE 9 (case 2 1c).—C. B., a woman of 23, was seen on Nov. 7, 1938 [*2*, chart 9], with the complaint of loss of sight in the left eye, discovered on awakening on November 2 [*1*, chart 9].

The onset occurred with the gradual development of maximally increased barometric pressure and immediately in association with the passage of a major cold air mass on the preceding day. The patient went to the physician at the succeeding barometric crest (*2*).

CASE 10 (case 4 [1c]).—M. T., a Negro man of 23, was seen on March 29, 1939 [*2*, chart 10], with a complaint of loss of sight in the right eye of three days' duration [*1*, chart 10].

Meteorologic associations in this case are striking, with the onset occurring with a sudden fall in temperature from the 70's (F.), this being followed by a further steep decline and a sharp accentuation of the symptoms, with admission of the patient at the barometric crest (*2*).

CASE 11 (case 5 [1c]).—M. S., a woman of 50, was seen on May 3, 1939 [*2*, chart 11], with the complaint of blurred vision in the right eye for two weeks [*1*, chart 11]. . . . The patient had two previous attacks of choroiditis. . . .

The onset of the disturbance had occurred at a time of environmental turbulence and marked precipitation; a barometric crest had been

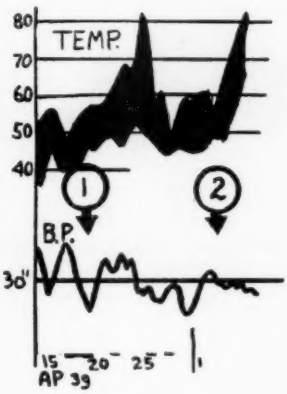

Figure 11

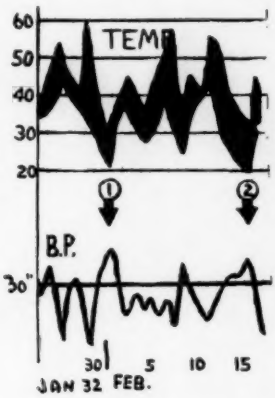

Figure 12

Chart 11.—Meteorogram to illustrate the clinical events in case 11.
Chart 12.—Meteorogram to illustrate the clinical events in case 12.

reached two days previously. The patient went to the physician at the end of the next period of cold, one day after the development of a barometric crest.

USE OF VASODILATORS IN TREATMENT OF RETROBULBAR NEURITIS

Finally, from Duggan's paper "Use of Vasodilators in Treatment of Retrobulbar Neuritis" I quote cases 12 and 13:

CASE 12 (case 6 [1d]).—J. J., a man aged 29, suffered from acute unilateral retrobulbar neuritis and multiple sclerosis. This patient, who was seen on Feb. 16, 1932 [*2*, chart 12], by Dr. Arnold Knapp, stated that he had an attack of sudden, complete blindness in the left eye fifteen days previously, with a slight return of vision since that time [*1*, chart 12].

When one examines the meteorogram in this case, one observes that the acute onset (*1*) occurred with a sharp rise in barometric pressure and an equally sudden drop in temperature. The patient came to the hospital for observation (*2*) during a similar environmental situation.

CASE 13 (case 7 1d).—R. K., a man aged 29, suffered from acute unilateral retrobulbar neuritis and multiple sclerosis. This patient . . . was seen on July 1, 1933 [2, chart 13], because of a complaint of sudden and complete loss of sight in the left eye which had occurred eighteen days before [*1*, chart 13]. He had also suffered from multiple sclerosis for two years.

On examination vision in the left eye was 3/200; the pupil showed hippus; the fundus was normal except for pallor of the temporal portion of the disk, and the field, by confrontation, showed a central scotoma about 15 degrees in diameter for a 10 mm. test object (nine days earlier vision had been restricted to perception of hand movements in the extreme peripheral field, and the pupil had not reacted

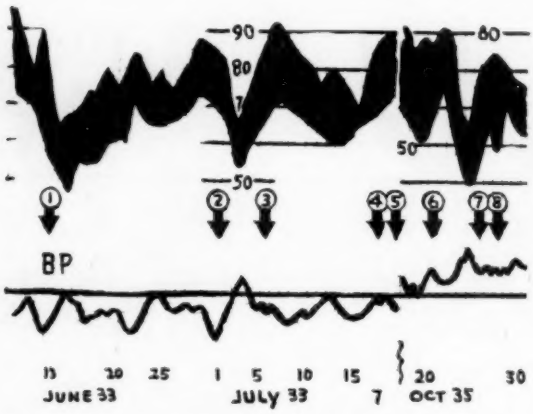

Chart 13.—Meteorogram to illustrate the clinical events in case 13.

to light). Vision in the right eye was 20/20 (corrected), and there were no abnormal findings except moderate myopia. The most prominent symptom of multiple sclerosis at this time was marked fatigabiltiy on exertion. The Wassermann reaction of the blood was negative, and there was no infection of the sinuses.

From July 1 to July 6 the patient was given six daily intravenous injections of sodium nitrite. Vision in the left eye showed improvement after each injection and was 20/25 after the sixth injection. The patient also volunteered the information that he was able to run after a trolley-car for the first time in two years.

Two weeks later he returned, stating that vision in his left eye had been failing again for two days.

When one examines the meteorogram in relation to these episodes, one notes that the onset of the disturbance (*1*) occurred when the temperature had dropped rapidly. The patient was seen (*2*) on a day when the temperature had increased rapidly and the barometric pressure had been unusually low. He was then given treatment until July 6 (*3*).

Whether the clinical improvement evident at this time was wholly due to the treatment or whether the accentuation of improvement was aided by a rapid exchange in environmental temperature would be a moot point. The patient returned two weeks later (*5*) stating that vision in the left eye had been failing for two days (*4*). Again one is dealing with a phase during which the barometric pressure had increased, but the temperature had also increased in this instance; the patient returned on October 28 (*8*) complaining of loss of control of the bladder, (*6*) and there had been blurring of the vision for two days previously (*7*).

Milliken and I [5] have previously called attention to the fact that clinical episodes that occur in the patient with multiple sclerosis are associated with change in the air mass. In this instance symptomatologic study amply confirmed this association. One notes that episode 6 occurred with a barometric crest and that the blurring of vision of which the patient complained (*7*) occurred immediately in the wake of a barometric crest and after the temperature had declined from a high of 80 F. to a low of 50 F.

THE UNDERLYING PATHOPHYSIOLOGY

In case 13, blindness occurred in one eye of Dr. Duggan's patient with multiple sclerosis on June 13, 1933, and it will be recalled that this occurred with the passage of a major polar air mass, the temperature declining from over 90 F. on June 9 to a low of 47 F. on June 15.

By analogy one can postulate that a vasomotor spasm, general as well as local, with the whole train of biologic adjustments thereby initiated,[6] precipitated the clinical event.

To demonstrate this sequence I turn to the clinical record of a patient with multiple sclerosis studied by us day by day in Chicago. The patient was a young Jewish man, with characteristic symptoms, observed from May 12, 1933 to the end of June.

A portion of the biometeorogram is reproduced in chart 14. The upper curve indicates the mean daily temperature; the next curve, that for the time of disappearance of methylene blue in the skin; the black field, the systolic and the diastolic pressure; the next three curves, the cholesterol content, the carbon dioxide content and the p_H of the blood; the black columns, the calcium, and the white columns, the potassium content; the following curve, the blood protein, and the last curve, the

5. Petersen, W. F., and Milliken, M. E.: Mental and Nervous Disease, in The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, Inc., 1934, vol. 3, chap. 12, p. 313.

6. Petersen, W. F., and Milliken, M. E.: Autonomic Integration, in The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, Inc., 1936, vol. 1, pt. 2.

capillary permeability. These curves portray the change that occurred in the patient at the time when the identical air mass concerned in case 13 passed over Chicago (dotted vertical line).

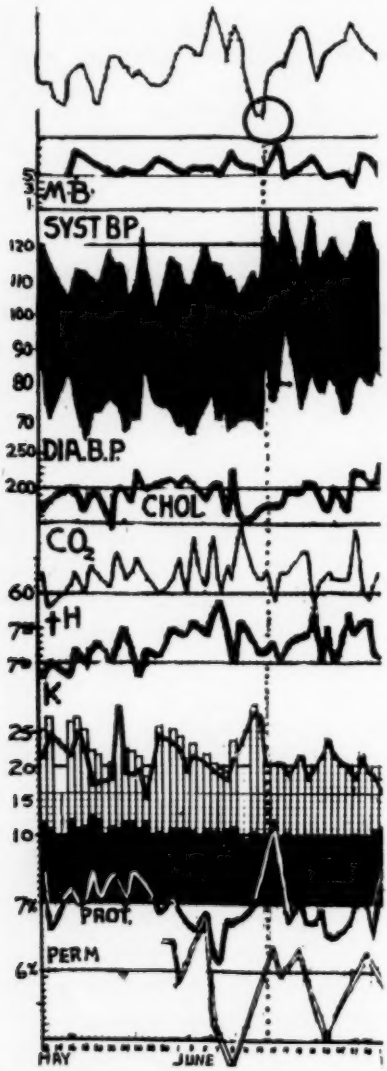

Chart 14.—Biometeorogram to illustrate a case of multiple sclerosis.

It is obvious that the significant increase in blood pressure, both diastolic and systolic, occurred coincidentally with a distinct fall in the carbon dioxide content, a striking fall in the potassium/calcium ratio and a marked increase both in the protein content of the blood and in

the capillary permeability. The time of disappearance of methylene blue was shortened, this change indicating the relative anoxia of the period.

In Dr. Duggan's patient similar changes must have taken place and the spasm was followed by local thrombosis—a common sequence of events. In the Chicago patient no such changes occurred, but a distinct increase in tremor was recorded.

COMMENT

In this paper the association of clinical precipitation of symptoms and change in the clinical course with change in the meteorologic environment has been demonstrated for diverse ocular disturbances. It has been made evident, too, that environmental situations normally associated with peripheral vasoconstriction and its resulting anoxia are almost invariably associated with initiation of the clinical episode or change in the clinical picture. Any extreme in the environmental situation, whether toward cold or toward undue heat, is apt to find reflection in clinical symptoms, for the simple reason that such changes entail major vasomotor adjustment.

While any one of many environmental factors—e. g., trauma, sensitization, emotion, infection—may act as a precipitating force, the weather episode, on the background of season, is the most common of the energy impacts that are effective, for the biologic effect is apt to be prolonged. The vascular spasm may exist for hours or even days, is subject to summation with repetition of environmental change and is, in addition, universal in its effectiveness in the population at large, though obviously the individual reaction will be modified by habitus, by shelter, by the condition of the individual, etc.

Effects such as those portrayed by Dr. Duggan, while spectacular because of their objectivity, should by no means confine the attention of the ophthalmologist or lead to the assumption that one is dealing with a special field of action. The meteorologic episode is universally effective, and the clinical reflection will be found in any organ or tissue.

CONCLUSIONS

An examination of Duggan's case records relates the precipitation of acute ocular episodes to the meteorologic status. The frequency of the change in the clinical condition with the passage of atmospheric fronts known to cause increase in the peripheral vascular tone, or spasm, confirms Duggan's thesis of the broad significance of vascular change in the underlying mechanisms of ocular pathophysiology.

1322 Astor Street.

LOCAL THERAPY OF CATARRHAL CONJUNCTIVITIS WITH SULFONAMIDE COMPOUNDS

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AND
ALSON E. BRALEY, M.D.
NEW YORK

There are now numerous reports in the literature describing good results from the direct application of the sulfonamide compounds in the prophylaxis and treatment of wound infections [1] and in the treatment of pyogenic cutaneous infections.[2] There are a lesser number of reports describing direct treatment with sulfonamide compounds of infections of the mucous membrane, particularly of the mouth, nose and throat,[3] but also of the eye [4] and the female genitourinary tract. In this connection, the field of external ocular infections has been incompletely explored, and at the time of writing no study of the effect of topical application in catarrhal conjunctivitis has appeared. The present study reports the results obtained in 512 cases of acute and chronic catarrhal conjunctivitis with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfadiazine (2-[paraaminobenezenesulfonamido]-pyrimidine) applied in ointment form.

METHOD OF TREATMENT

The sulfonamide compounds have been used locally in solution, powder, emulsion and ointment forms. In view of their rapid dilution by tears, solutions would appear to be of limited value for use in the conjunctival sac unless applied extremely frequently. Furthermore,

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Read at the Seventy-Eighth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 2, 1942.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

1. Hawking, F.: Experimental Use of Sulfonamides in Prevention of Gas Gangrene, Brit. M. J. **1**:263, 1941.

2. Pillsbury, D. M.; Wammock, V. S.; Levingood, C. S., and Nichols, A. C.: The Local Treatment of Pyogenic Cutaneous Infections with Sulfathiazole, Am. J. M. Sc. **202**:808, 1941.

3. Turnbull, F. M.: Intranasal Therapy with Sodium Salt of Sulfathiazole in Chronic Sinusitis, J. A. M. A. **116**:1899 (April 26) 1941.

4. Guyton, J. S.: Local Use of Sulfanilamide Compounds in the Eye, Am. J. Ophth. **24**:292, 1941.

because of the low solubility of sulfathiazole and sulfadiazine, it is necessary to use solutions made with the sodium salts of these drugs, and these, because of their alkalinity, may cause irritation on prolonged use. Powder can be used successfully in the treatment of hospitalized patients but is not practical for ambulant patients. Emulsions have an advantage over ointments in that the drugs are released more rapidly, but patients find them irritating and complain of crusting of the lid margins, which occurs with drying. Ointments have the advantage of permitting prolonged action of the drugs and are well tolerated. A few patients have complained of the slight blurring produced by the film of ointment, but this would seem to be a minor discomfort. For

TABLE 1.—*Persistence of Sulfathiazole in Epithelial Scrapings from Rabbit Conjunctivas After a Single Application of the Drug in Various Bases* *

(Data averaged from tests on 7 rabbits)

No.	Type of Ointment	15 Min.	30 Min.	60 Min.	2 Hr.	3 Hr.	4 Hr.
1	5% sulfathiazole, 25% hydrous wool fat and 75% petrolatum	+++	+++	++	+	—	—
2	5% sodium sulfathiazole, 25% hydrous wool fat and 75% petrolatum	+++	++	++	+	Trace	—
3	5% sulfathiazole, 50% hydrous wool fat and 50% petrolatum	+++	++	++	Trace	—	—
4	5% sulfathiazole in hydrous wool fat	+++	+++	+++	++	+	Trace
5	5% sulfathiazole in K-Y lubricating jelly	++	+	Trace	—	—	—
6	5% sulfathiazole in a vanishing cream base	+	—	—	—	—	—
7	5% sulfathiazole, 12% triethanolamine, 10% glyceryl monostearate, 4% glycerin and 2% cetyl alcohol	++	+	Trace	—	—	—

* Strong positive reaction for sulfathiazole, +++; good positive reaction for sulfathiazole, ++; weak positive reaction for sulfathiazole, +; trace, slight positive reaction for sulfathiazole.

the purposes of this study ointments were used exclusively, the ointment base consisting of 25 per cent hydrous wool fat and 75 per cent petrolatum.

Three sulfonamide drugs, sulfanilamide, sulfathiazole and sulfadiazine, were used first in concentrations of 1 per cent and 5 per cent. Since the 5 per cent concentrations were well tolerated, the 1 per cent were discarded. In a few instances concentrations up to 25 per cent were tried, but these appeared to produce from mild to moderate conjunctival irritation. Sulfanilamide was used in the preliminary studies but appeared to be definitely less efficacious than sulfathiazole or sulfadiazine and so was discontinued. Since in vitro studies [5] indicated a

5. Gallardo, E.: In Vitro Action of Sulfonamide Drugs on Conjunctivitis-Producing Bacteria, to be published.

bacteriostatic action against most of the conjunctival bacteria slightly greater for sulfathiazole, this was the drug chosen for routine use. Both sulfathiazole and sodium sulfathiazole were employed, but no difference in efficacy between the two was observed.

The desirability of maintaining a more or less constant bacteriostatic concentration of the sulfonamide drugs throughout the period of treatment has been emphasized repeatedly. In an attempt to estimate how frequently ointment should be used we tested the persistence of sulfathiazole on the conjunctiva of the rabbit after single applications of it in various ointment bases. Conjunctival scrapings were taken at intervals up to four hours and tested for the presence of the drug. Table 1 records the data averaged from tests on 7 rabbits for each of the bases. It will be seen that in rabbits tested with the base used in this series (no. 1) there were traces of sulfathiazole two hours after application of the drug. Although these results are not directly transferable to the human eye, they would seem to indicate that ointment should be used more frequently than is customary.

Available for study were cases of acute and chronic conjunctivitis at Vanderbilt Clinic and at Letchworth Village, a state institution for mentally deficient children about 30 miles from New York city.

TREATMENT OF ACUTE CATARRHAL CONJUNCTIVITIS

At Vanderbilt Clinic 126 cases of acute catarrhal conjunctivitis were studied. In 69, 5 per cent sulfathiazole ointment was used, and in 57, as controls, clinical applications of 1 per cent silver nitrate and home use of 1 : 5,000 mercury oxycyanide solution were employed. All cases were studied by smear or epithelial scrapings and by culture; with the exception of one beta hemolytic streptococcus and two coliform rods, only three conjunctival pathogens, Haemophilus influenzae, Diplococcus pneumoniae and Staphylococcus aureus, in this order of frequency, were observed. The disease healed rapidly in all cases in both groups except those in which it was caused by the staphylococcus. In 14 of the 26 cases of staphylococcic conjunctivitis treated with sulfathiazole the disease healed rapidly without recurrence, but in the remainder it required up to twenty-five days for cure. This finding is in contrast to that for the 22 cases of staphylococcic conjunctivitis treated with silver nitrate and mercury oxycyanide, in 9 of which the infection became chronic and required many months for healing.

Since nonstaphylococcic acute catarrhal conjunctivitis is known to be self limited and responsive to most common antiseptics, therapy with sulfonamide compounds would appear to offer no special advantages over ordinary therapy. Unfortunately, however, the staphylococcic

form cannot be recognized except by smear or culture, and in view of the frequency with which it occurs and its tendency to chronicity, intensive treatment with sulfathiazole in all cases of acute catarrhal conjunctivitis of bacterial origin would seem to be indicated.

TREATMENT OF CHRONIC CATARRHAL CONJUNCTIVITIS

Chronic conjunctivitis has always been a therapeutic problem, and none of the therapeutic measures employed up to now have been entirely successful. The problem is of particular importance at the present time, because of the frequency and severity of chronic conjunctivitis in the Near East and in the Orient, where United States troops will soon be stationed in large numbers. Letchworth Village,

TABLE 2.—*Organisms Encountered in Cases of Catarrhal Conjunctivitis at Letchworth Village*

Organism	Cottage Theta	All Other Cottages
Diplobacillus	27 *	67
Staphylococcus aureus	31	56
Staphylococcus albus	33	39
Haemophilus influenzae †	18	49
Pneumococcus	7	15
Streptococcus viridans	15	16
Neisseria catarrhalis	14	17
Corynebacterium xerosis	35	10
Streptococcus haemolyticus	3	4
Friedländer's bacillus	6	0
Coliform rods	1	7

* The figures show the number of cases in which bacteria were observed.

† For the purpose of this study, no distinction was made between the influenza bacillus and the Koch-Weeks bacillus.

where chronic conjunctivitis has been particularly troublesome, offered unusual opportunities for testing the efficacy of topical applications of the sulfonamide drugs.

The children at Letchworth Village are segregated in cottages according to sex and mental condition. Cottage Theta, occupied by boys and young adults of the higher mental grades, was most heavily affected by conjunctivitis, 86 of the 128 inmates having chronic conjunctival disease at the time of our studies. Table 2 records the bacteriologic data for their cases. Treatment with mild protein silver and yellow mercuric oxide as prescribed by the institution physicians proved over a period of many months to be incapable of influencing the disease. In view of the high frequency of diplobacilli, we tried 0.5 per cent zinc sulfate ointment, but with almost complete lack of success. This unexpected failure is believed to have been due to the fact that mixed infections, particularly of Staph. aureus with the diplobacilli, were almost the rule and Staph. aureus appears to be virtually unaffected by zinc therapy.

Therapy with sulfathiazole ointment, on the other hand, proved remarkably effective in controlling the disease, in spite of the handicap that treatment could be given only twice daily because of insufficient nursing help. Of the 72 cases of chronic conjunctivitis, the condition was controlled in all except 14 cases of trachoma and 1 case of cicatricial ectropion. There were 7 cases in which the disease recurred during the twelve months' observation period, but the recurrences were easily controlled by readministration of the drug. In 12 of the 14 cases of trachoma this disease healed or became greatly improved with oral sulfanilamide therapy. The results in Cottage Theta were particularly gratifying because of the high incidence of blepharitis, a complication which had rendered treatment at the Vanderbilt Clinic much more difficult.[6]

Chronic conjunctivitis of bacterial origin in 147 cases in sixteen other cottages at Letchworth Village was similarly treated, with 5 per cent sulfathiazole ointment, and in all but 32 cases responded satisfactorily, although more slowly when associated with blepharitis. Of the 32 cases of resistant infection, there was underlying trachoma in all but 1; in most the exudate was diminished, probably as a result of the action of the sulfonamide compound on the secondary bacterial infection, but the trachoma itself remained unaffected.

In addition to the cases at Letchworth Village, a series of 188 cases of chronic conjunctivitis of bacterial origin at Vanderbilt Clinic were selected for study. The infection was staphylococcic in all except 1 case of mixed diplobacillary and staphylococcic infection and 1 case in which a Proteus organism was demonstrated. Of the 188 cases, the disease in 54 was treated by ordinary antiseptic methods, including application of silver nitrate in the clinic and use of one or more of the following medications at home: 1:5,000 mercury bichloride ointment, 1:5,000 mercury oxycyanide solution, 0.25 per cent zinc sulfate solution and 2.5 per cent ammoniated mercury ointment. In this group there were 6 cases in which the infection healed, 31 in which it improved satisfactorily but did not become entirely healed and 16 in which it failed to show improvement. On the other hand, in 128 of the 133 cases in which sulfathiazole was used there was pronounced improvement or cure. In the only case of proteus conjunctivitis, the infection failed to respond to local treatment with sulfathiazole but became clinically healed with oral administration of sulfathiazole; later it recurred.

In an additional series of 40 cases of chronic conjunctivitis, in which no significant bacteria could be found, 5 per cent sulfathiazole ointment was used with little or no improvement.

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6. Thygeson, P.: Staphylococcic Blepharitis, Tr. Am. Acad. Ophth., to be published.

ALLERGIC REACTIONS TO LOCAL THERAPY WITH SULFONAMIDE COMPOUNDS

In the course of these studies a number of sensitivities to sulfathiazole ointment were encountered. These differed in no way from similar sensitivities to other drugs, such as butyn, phenacaine and mercury, and were characterized by conjunctival inflammation, dermatitis of the eyelids and itching and a conjunctival eosinophilia. The reactions disappeared rapidly when the drug was discontinued. There were no cases of sensitivity to sulfadiazine ointment and only 1 of sensitivity to sulfanilamide. There appeared to be no cross sensitivity among the three sulfonamide compounds. The sensitivity usually occurred only after prolonged use of the drug. The only exception was in a case in which a cutaneous rash had previously developed after oral sulfathiazole therapy.

COMMENT

On the basis of results obtained in this study it is believed that in the majority of cases of conjunctivitis, both acute and chronic, in which the ordinary conjunctival pathogens are causal, the disease should respond readily to adequate local therapy with a sulfonamide compound. In this series the cases in which the conjunctivitis was resistant to sulfonamide compounds could be grouped into three classes: (1) those in which severe blepharitis or involvement of the meibomian glands was present; (2) those in which there was an underlying nonbacterial infection, such as trachoma, and (3) those in which no bacteria were observed.

The results obtained in the treatment of conjunctivitis in the cases at Cottage Theta in Letchworth Village are believed to be of particular significance. In these cases sulfathiazole ointment was effective in controlling chronic conjunctivitis which had reached epidemic proportions and which had failed to respond to ordinary treatment over a long test period. The ointment as used twice, or at most three times, daily did not prevent recurrences, but these, except in a very few instances, were easily controlled by a second course of therapy. The significance of these results for the prophylaxis and treatment of epidemic bacterial conjunctivitis such as might occur among United States troops in the Near East and in the Orient is obvious.

As was expected, sulfathiazole ointment had no effect in the cases of trachoma in this series, although that disease responded readily to sulfanilamide administered orally. There is no apparent reason, however, why topical applications of the sulfonamide drugs should not be successful in trachoma provided they are made frequently enough to maintain a constant therapeutic concentration throughout the period of treatment. The frequency required to accomplish this end, however, is not practical for nonhospitalized patients.

SUMMARY AND CONCLUSIONS

In a series of 512 cases of acute and chronic conjunctivitis at Vanderbilt Clinic and Letchworth Village, local therapy with sulfonamide compounds was employed.

Acute catarrhal conjunctivitis of bacterial origin responded satisfactorily to treatment with 5 per cent sulfathiazole ointment. This treatment appeared to be of particular value in acute staphylococcic conjunctivitis, which under ordinary methods of treatment frequently becomes chronic.

Chronic conjunctivitis caused by Staph. aureus and diplobacilli, unmixed or mixed with other conjunctival pathogens, responded satisfactorily to treatment with sulfathiazole ointment. Mixed staphylococcic and diplobacillary conjunctivitis which had been completely resistant to zinc sulfate yielded readily to sulfathiazole ointment. Ordinary antiseptic therapy was relatively ineffective.

Chronic conjunctivitis in which there were no significant bacteriologic pathogens failed to respond, with a few exceptions, to local therapy with a sulfonamide compound.

A few local allergic reactions to sulfathiazole were encountered.

Dr. Harry C. Storrs, superintendent of Letchworth Village; Dr. James K. Petit, assistant superintendent, and Dr. Edward Humphreys, director of research, cooperated in this study.

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CONGENITAL ABSENCE OF LACRIMAL PUNCTA IN THREE MEMBERS OF A FAMILY

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Absence of puncta is of interest because of its rarity and the various operative technics which have been devised for its correction.

According to Ida Mann,[1] the sac and nasal duct are developed as a line of buried epithelium formed by the overlapping of the lateral nasal process by the maxillary process. The tucked-in epithelium separates from the surface and by budding from its upper end maps out the canaliculi and puncta. All the passages are at first blocked out in solid epithelium and do not canalize until just before birth. The passages do not develop, the epithelial buds pursue an abnormal course or the apparatus fails to canalize.

Failure of canalization leads to congenital lacrimal obstruction and, since the epithelial plug invariably becomes infected during or just after birth, to congenital dacryocystitis.

The two epithelial extensions which pass from the sac to enter the upper and lower lid folds and form the canaliculi and puncta may fail to bud out at the 17 mm. stage, so that the canaliculi are absent. More commonly, they form but fail to reach the surface, so that the puncta above are absent. More often still, the position of the puncta can be seen on the surface as small dimples, which just fail to connect with the underlying canaliculi and can easily be made to open into them. This is known as atresia of the puncta.

An effort should be made to distinguish between cases of atresia and those of complete absence of the puncta, as the method of treatment is different.

In a review of the literature 21 cases of absence of puncta and canaliculi have been found. There have been no previous reports of this congenital defect occurring in more than 1 member of a family, although in 1 case a similar condition was present in a grandfather. In the family to be reported on here, puncta were absent in a father and 2 siblings.

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Read before the New York Academy of Medicine, Section of Ophthalmology, May 18, 1942.

1. Mann, I.: Developmental Abnormalities of the Eye, New York, The Macmillan Company, 1937, p. 415.

It is interesting that Burnett [2] quoted von Walther as saying, "Atresia of the puncta and the beginning of the canals, aside from monopsia and micropsia, is not to be met with as a congenital defect."

In 1846 Blanchet [3] presented a patient in whom all four puncta were missing, as did Emmert [4] in 1877.

Magnus [5] described a youth in whom both lower puncta were absent and the upper puncta were well developed. He also reported on a girl with the same condition.

In 1884 Burnett [2] noted absence of both puncta on the left side and of the lower punctum on the right in a boy aged 10. He was able to make an incision into the canaliculi and cure the epiphora.

Von Reuss [6] described a boy in whom the papillae were present but all four puncta were absent.

Fieuzal [7] reported a case of total absence of all four puncta, as did De Wecker and Landolt [8] in their textbook. They mentioned the point that complete absence of the lacrimal puncta usually coincides with absence of the lacrimal glands. This has not been confirmed by other authors.

Cabannes [9] described a patient who lacked puncta in the lower lids.

Fox [10] was able to make slits in the canaliculi of a boy and insert a cannula which carried away the tears.

Ferron [11] in 1892 reported the total lack of puncta in a girl.

Lafite [12] observed a girl with complete absence of the puncta on the left side and of the lower punctum on the right. The patient's mother and grandmother had always suffered from lacrimation, and a brother had been operated on for a cyst of the lacrimal sac which had developed in connection with imperforation of the canaliculus on that side.

Lebègue [13] described 5 cases in which were observed absence of various of the puncta.

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2. Burnett, S. M.: Arch. Ophth. **13**:53, 1884.

3. Blanchet: Bull. Acad. de méd. **12**:621, 1846-1847.

4. Emmert, E.: Arch. Ophth. & Otol. **6**:525, 1877-1878.

5. Magnus, H.: Klin. Monatsbl. f. Augenh. **13**:199, 1875.

6. von Reuss, A.: Wien. med. Presse **27**:205, 1886.

7. Fieuzal, T. E.: Bull. clin. nat. opht. de l'hosp. d. quinze-vingts **5**:195, 1887.

8. de Wecker, L., and Landolt, E.: Traité complet d'ophthalmologie, Paris, A. Delahaye et Cie, 1889, vol. 4, p. 1057.

9. Cabannes: Arch. d'opht. **16**:423, 1896.

10. Fox, L. W.: Ophth. Rec. **9**:403, 1900.

11. Ferron, L.: Bull. Soc. d'anat. et physiol. de Bordeaux **13**:87, 1892.

12. Lafite: Bull. Soc. d'anat. et physiol. de Bordeaux **16**:34, 1895.

13. Lebègue, P.: Anomalies et maladies congénitales des voies lacrymales, Thesis, Paris, 1910.

Kraupa [14] added a case in which the right upper punctum was absent as well as the left upper and lower. He made an incision between the caruncle and the crescentic fold into the sac, causing a cure of the lacrimation.

Blackmar [15] reported on a boy with all four puncta absent as well as the canaliculi.

Goar [16] described a case in which there was a complete absence of the puncta and papillae on the left side and of the lower canaliculus. He made an incision through the semilunar fold behind the caruncle and dissected through the lateral wall of the sac. The opening was kept patent by means of frequent passing of Bowman probes.

McCoy [17] found an absence of puncta on both sides in a boy aged 5.

Cameron [18] was unable to find any signs of puncta or lower canaliculi in a boy. The grandfather also revealed an absence of puncta. An opening was made lateral to the caruncle and a Bowman probe inserted, but the opening did not remain patent.

REPORT OF CASES

The cases forthwith presented are of interest because of the absence of puncta in a father and 2 children.

CASE 1.—The father showed absence of both upper puncta. The right lacrimal sac was removed in 1934. In 1923 a slit had been made in the right lower punctum.

CASE 2.—One child, a boy aged 7, was admitted to Bellevue Hospital on July 8, 1941 and operated on on July 9. As long as the parents could remember, tears had run down his cheeks. On the second day after birth, pus was noticed in each eye. A progressive swelling was lanced when he was 5 weeks old. The eyes were then quiet until 1935, when an abscess formed, which was lanced. In May 1941, during pneumonia, swelling and pus again were present. On his admittance to Bellevue Hospital in July 1941, a suppurative draining fistula was present on each side of the face between the nose and the inner canthus of the eye. Swelling, pain, redness and tearing were present on both sides.

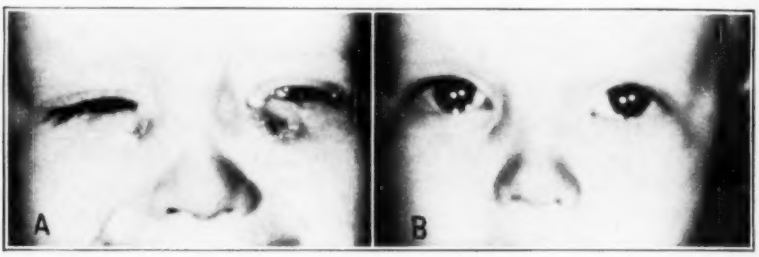
Vision in the right eye was 16/50+2 and in the left 16/30. In the right eye the upper punctum was present and the lower punctum was absent. In the nasojugal fold 6 mm. below the inner canthus there was a fistula of the lacrimal passages draining clear mucopurulent material. There were a few small keratoses about and below the fistula along the nasojugal fold. No swelling was noted over the lacrimal sac. The conjunctivas, cornea, anterior chamber, iris and lens were normal. In the left eye the upper punctum was absent and the lower punctum was present. There was a fistula of the lacrimal passage 5 mm. above the inner canthus at the site of a red, indurated, elevated mass 6 mm. in diameter extending deep along the nasal wall of the orbit inferiorly to the level of the

14. Kraupa, E.: Klin. Monatsbl. f. Augenh. **48**:445, 1910.
15. Blackmar, F. B.: Am. J. Ophth. **8**:139, 1925.
16. Goar, E. L.: Tr. Am. Ophth. Soc. **29**:91, 1931.
17. McCoy, L. L.: Am. J. Ophth. **15**:636, 1932.
18. Cameron, W.: Am. J. Ophth. **17**:432, 1934.

canthal ligament. Irrigation through the lower punctum expressed yellow pus followed by clear mucoid material from the fistula above. The conjunctivas were red; the cornea, anterior chamber, iris and lens were normal. Both disks were a pale pink with the retinal vessels branching out in normal ratio. The maculas were seen, and no lesions were present. The muscles showed 35 prism diopters of esotropia at 13 inches (33 cm.) and 27 disk diameters of esotropia at 20 feet (610 cm.). Smears of pus from the fistulas showed Streptococcus haemolyticus, Staphylococcus and Bacillus subtilis.

With the child under ether anesthesia, methylene blue was injected into the external lacrimal fistula of the right eye. A cutaneous incision was made over the fistulous area. The section was deepened down to the anterior lacrimal crest. The sac was dissected and excised. The bony wall was curetted. A probe was inserted through the nasolacrimal duct into the nose. Catgut sutures approximated the medial canthal ligament. The cutaneous incision was closed with black silk sutures. A similar procedure was carried out on the left side. On this side a probe could not be passed into the nose.

CASE 3.—The second child, a boy, was admitted to Bellevue Hospital on March 16, 1942 with the complaint and the general appearance much the same as those



A, patient 3 before operation, showing bilateral fistulas. *B*, patient 3 after operation.

of the first child. At the age of 20 months he had been admitted to the pediatrics clinic with bronchial pneumonia. After a critical course he was cured, and he left the hospital at the end of two weeks. At that time a little discharge of pus was noted in both eyes. In January 1941 he was readmitted for treatment of nasal pharyngitis, conjunctivitis and absence of both upper puncta. In two weeks he was discharged, having recovered from the infection of the upper respiratory tract. On March 16, 1942 he was readmitted. Swelling, tenderness and purulent discharge from both sac regions were present. The right sac had spontaneously opened, and there was a copious purulent discharge.

With the child under general anesthesia, the lacrimal passages were injected with iodized oil for x-ray examination. On March 23 bilateral dacryocystectomies were performed, during which it was discovered that there were numerous aberrant passages present. Methylene blue was injected through the fistulous openings, and the infected tracts were completely excised. The patient was discharged April 2 after an uneventful recovery.

In all 3 cases there is some epiphora, but the infectious processes appear to be cleared up.

140 East Fifty-Fourth Street.

DISCUSSION

DR. DANIEL B. KIRBY: The congenital anomalies reported are interesting, and from the appearance before operation one can judge that the cases have been well handled. In the average case of atresia of the duct, one finds a lacrimal sac. One can probe this and open it. In the cases reported, there was no possibility of establishing drainage into the nose. There was no lacrimal groove, and if any connection had been made with the nasal mucous membrane, probably only a fistula would have resulted. Moist eyes are not dangerous eyes, but if the epiphora is too annoying, it may be possible to resect a portion of the lacrimal gland. It is wise not to try irradiation of the lacrimal gland to diminish lacrimal secretion.

PRACTICAL APPLICATION OF CROSSED PRISMS

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The crossed prism test can be used for both heterophorias and heterotropias and in all the cardinal positions, but I shall discuss only its use in the primary position, for near vision, 13 inches (33 cm.), and for distant vision, 20 feet (610 cm.).

Of course, the muscles should be studied in all the cardinal positions for the proper diagnosis of any imbalance. The interpupillary distance for both near (13 inches) and distant (20 feet) vision is determined and the trial frame adjusted accordingly. The refraction for all patients under 40 years of age is done with a cycloplegic unless contraindicated.

With the proper correction in place to render the eyes emmetropic or as nearly so as possible, while the patient is still under the cycloplegic the test is performed for distant vision. It is repeated after mydriasis with the prescription in place, both for near and for distant vision.

With the Maddox disk over one eye and the patient fixing on the test light, the examiner slowly revolves the rod until the light streak cuts the light. (If it cuts the light all the way around, there is no muscle imbalance.) He then takes the degree reading on the frame and revolves the rod 90 degrees from this point. The streak will then be at its farthest point from the light. This reading will be the direction of the imbalance and the position at which the neutralizing prism will have to be placed. By slowly increasing the strength of the prisms, placed with their bases toward the primary position of the eye, until the light streak cuts the light, the exact prism strength and position are determined. To prevent the usual errors one gets by using the Maddox rod, it is necessary always to use the cover test in conjunction with it. The Maddox rod can then be revolved, and it will cut the light in all positions.

A fixed imbalance, caused by some types of paralysis, or a mechanical imbalance, resulting from exostosis of the orbit or following an accident, must be completely corrected if the visual power of the eyes is sufficient to give binocular fixation.

Some patients with heterophoria need no prismatic correction. Some should have a partial but practically none a complete correction. A complete diagnosis of the status of the muscles along with a description of the symptoms will help the ophthalmologist to formulate his final prescription for prismatic correction.

The test may be illustrated as follows: G., aged 40, had for the right eye a correction of + 0.50 D. sph. ⊃ with 4 D. of prism base down and 7 D. of prism base in.

As in figure 1, draw line *ZY*, consisting of 4 units of measure perpendicular to line *YX*, consisting of 7 units of measure at *Y*. Line *XZ*, which in this instance happens to be approximately 8 units of measure in length, determines the strength of the resultant prism, which would determine the position of the near prism in relation to *YX*, which in this instance happens to be 30 degrees.

The length of *XZ*, of course, is determined by the square root of the sum of the squares of the other two sides of triangle *XYZ*. This is approximately 8 degrees.

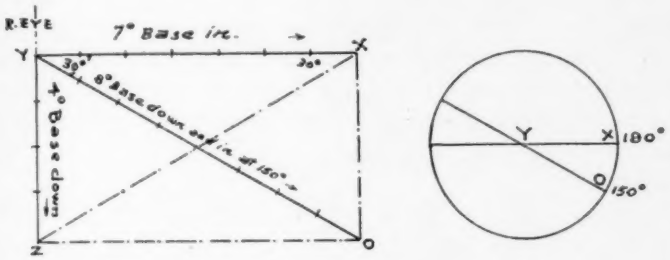

Fig. 1.—Estimation of prism strength position.

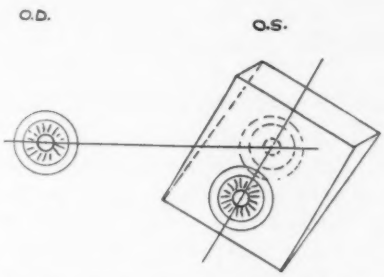

Fig. 2.—Prism position to correct the heterophoria and heterotropia.

Therefore, in this case, the final prism would be an 8 degree prism 30 degrees from the position of the greater prism toward the position of the lesser prism. Since the greater prism is at the 180 degree angle, the resultant prism would be at a 150 degree angle base down and in, as *YO*.

The strength of the resultant prism is always greater than that of either of the other two, and its position is nearer to the base of the stronger prism and always lies between the bases of the other two.

This is a complete prism correction of the muscle imbalance, which can be divided into heterotropia and heterophoria by the cover test with prisms to determine the heterotropia. I wait until this stage to determine the heterotropia so that I may know the direction in which

to hold the neutralizing prism. If the eyes are then checked with prisms in the six cardinal positions and their ductions are estimated, the prescription lenses, prisms for continuous wear or for exercise, an operation or a combination of all or a part of these can be determined on for the proper handling of the case. I am assuming that no infection, tumor or mechanical condition is complicating the picture.

I have not stated that the full correction should be prescribed, as the prescription depends on the ophthalmologist's judgment after a thorough study. All, none or a fraction of the correction may be used.

Many things must be kept in mind. Ocular deviations are always greater if the fixing eye is the one with the weaker extraocular muscles. The fixing eye is easily determined in cases of alternating squint, in which, as a rule, the eye without the Maddox rod does the fixing. By placing the rod over one eye and testing the other with the prisms, one is bound to observe a difference. The thickness of a prism before one eye may cut down the visual acuity enough to render the other eye the fixing eye.

The results of tests of phoria vary at different times of the day and even on different days, depending on the alertness and muscle tone of the patient at the time.

I hope this discussion clears up much of the confusion attached to the prescribing of vertical and lateral prisms and the complex methods of figuring out the resultant prism strength and position.

FAST WAY TO DETERMINE THE WEAK MUSCLE

Have a special trial frame with the eye piece rather large and fitting snugly against the skin. Then, with a semicircular rod (of the Maddox type) in a semicircular disk properly centered over the eye, revolve the disk in the six cardinal directions while placing the light in these positions and determine in which one the streak is farthest from the light. This position will be the field of action of the weakest muscle. As the image from the weak eye always runs away, it is easy to tell which eye is the weaker. The cover test must be used in conjunction with this test for it to be of any value.

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CORRECTION OF LOW ASTIGMATISM

SUBTRACTION TEST

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There is no agreement about the importance of cylindric errors, and experts differ widely as to how completely they should be corrected. Particularly is this true regarding low power errors. Many authorities make it a practice to undercorrect high astigmatism, and some consider it fussy to pay much attention to errors under 1 D. Abroad, especially, this is considered good practice. In some parts of this country, on the contrary, the teaching is that low errors cause disturbances out of all proportion to their size. Recently Prangen had occasion to take issue with the still more extreme doctrine that small errors are actually more disturbing than large ones. It will be noted that such theories do not take into consideration the fact that patients differ completely in their reaction to the same amount of astigmatism. Some ophthalmologists must share my experience that it is not the size of the error but the response of the patient that determines the need for correction of a low error. There is, for instance, on the one hand, a woman of 50 who seldom uses her distance correction, containing well over 1 D. of cylinder, unless driving or at the moving pictures. Such patients are not uncommon. All practitioners run across patients who, wearing 0.5 D. of cylinder with the axis transposed by an optician so that the error is actually doubled, like their glasses and have returned for more. On the other hand, the exact opposite may be true of more susceptible subjects, for example, an office nurse who becomes queasy when reading without a pair of weak cylinders (right eye, + 0.50 D. cyl., axis 100; left eye + 0.37 D. cyl., axis 75). My contention is that the response to a low amount of astigmatism is an attribute of the individual patient. It is not the amount of the cylinder or the experience of the examiner but purely the degree of sensitivity of the patient that counts.

If one must have rules, one may say, (1) that low astigmatism is more distressing to a sensitive patient than a gross cylindric error to a stolid one; probably no one would question the further claim (2) that low errors of astigmatism are both more numerous and more elusive than higher ones.

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High astigmatism is readily estimated by any standard method. It is the low errors that require finesse on the part of the examiner. For detecting low astigmatism I have for a long time made use of a fast and simple method. It is a variant of standard technics. At one time I tried hopefully to explain it in graduate teaching as the "subtraction test." It was soon apparent, as pointed out by John Green, that my description was too condensed. However, I occasionally find it used in testing for power. It is obvious and elementary; so maybe other examiners have worked it out for themselves. Before the test is applied, the patient's error is estimated, usually by retinoscopy. A cycloplegic may have been administered, though the technic is also useful in "dry" refraction. The correction disclosed is set up in the trial frame. The subtraction test differs from the conventional method of improving, or refining, this correction. That is, it is not performed by holding in front of the trial frame lenses an auxiliary low plus cylinder turned first to the axis of the trial frame cylinder with the query "Is this better or worse?" and then turned to a right angle to it with the same question. The objection to this procedure is that the patient is apt to reject the auxiliary plus cylinder no matter whether he needs it or not. There are two reasons for his rejecting it: (1) the familiar aversion of an eye for a total plus correction and (2) the presence of the added thickness of glass, which is apt to nullify any benefit from the improved correction. The "glass factor" is occasionally made evident by a patient who reveals that he is trying to make allowance for blurring which he attributes to dust or grease on the lenses. Neither does the test make use of an auxiliary minus cylinder similarly turned first to the trial frame axis with the inquiry "Better or worse?" and then reversed 90 degrees. In both instances the patient is puzzled to know how much blurring to allow for when the auxiliary lens is added.

THE SUBTRACTION TEST FOR POWER

To avoid this difficulty, the subtraction test makes comparison between two identical auxiliary cylinders. The glass factor is then present but is the same in both diameters. In this procedure (1) the patient's estimated correction is set up in the trial frame, in the manner described; except that (2) the spherical element usually has about +0.25 D. of overcorrection (or of undercorrection if minus); (3) astigmatism is corrected with a plus cylinder; (4) two minus cylinders (—0.37 or —0.50 D.) are taken, one in each hand, one of the auxiliary cylinders being at the axis of the trial frame cylinder and the other at right angles to it, and (5) alternation of these cylinders in front of the trial frame correction makes comparison easy and accurate. The patient

is asked to choose between the two cylinders. It is immaterial whether either improves the vision. Both may even depress it. Sometimes it is advantageous to word the inquiry, "Which of these is the worse?" The problem is which, if either, is better than the other, not which one improves the trial frame correction.

I. If the patient accepts the auxiliary minus cylinder at the plus axis of the trial frame correction, it "subtracts" from the trial frame cylinder, which, therefore, has to be reduced. II. If, on the other hand, the adverse axis, which augments the cylindric portion, is preferred, the trial frame cylinder must be increased. III. If there is no choice, the trial frame cylinder cannot be improved and is correct as it stands. IV. This

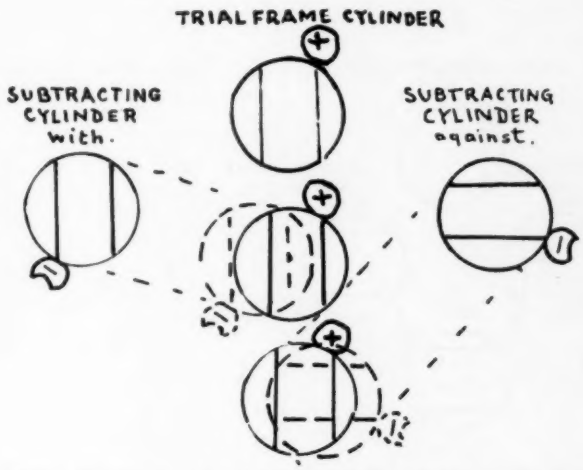

Fig. 1.—Test for power. A trial frame plus cylinder set at a predetermined axis is tested for power by alternating before it two equal minus cylinders, the first at the same axis and then the other at the perpendicular axis.

is the result to be aimed at; so the amount of cylinder is increased or decreased until there is no choice between the auxiliary minus cylinders.

DETERMINATION OF AXIS

The subtraction test can also be used to locate the axis when this is unknown. The technic outlined is then applied at each of the four cardinal axes. First the spherical correction, slightly generous if plus and scant if minus, is placed in the rear cell of the trial frame. Then in the front cell is added a + 0.25 D. cylinder at axis 90. In front of this the auxiliary minus cylinders are alternated in the manner described. The trial frame cylinder is rotated to 180, to 45 and finally to 135. At

each position the alternation of the auxiliary cylinders is repeated. The interpretation is exactly what would be expected.

I. There Is No Astigmatism.—It may be found that the plus cylinder is rejected at every axis. Such rejection is shown by acceptance of the minus cylinder at the same axis as the plus cylinder in all four cardinal positions. Then no astigmatism exists at any axis.

II. Astigmatism Exists at a Cardinal Axis.—If, however, there is one cardinal axis at which the plus cylinder is not so rejected, that is the axis at which there is astigmatism. The signal may take either of the two forms described under the heading "The Subtraction Test for Power." A. If there is no choice between the two minus cylinders, then astigmatism exists at this axis but is properly corrected by the plus 0.25 D. cylinder already in place. B. But if the minus cylinder is preferred

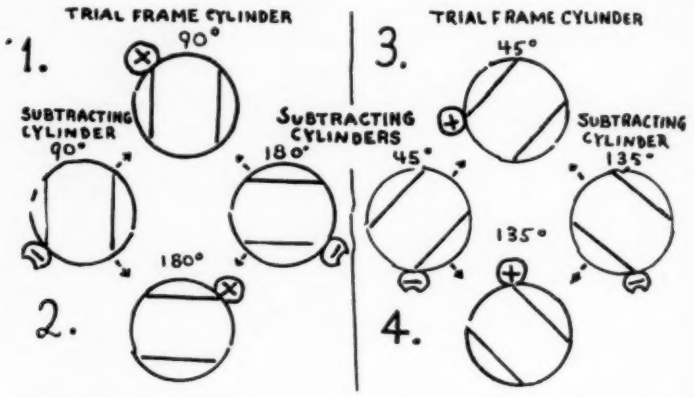

Fig. 2.—Test for axis. The test for power is repeated at the four cardinal axes.

at the axis perpendicular to that of the plus 0.25 D. trial frame cylinder, then more astigmatism exists at this axis than has been corrected. The latter is always the stronger signal.

III. There Is Astigmatism at an Intermediate Axis.—Astigmatism of course does not have to fall exactly on a cardinal axis. So if a signal is found at two cardinal axes, the true axis is to be looked for somewhere between them. A. If the signal is equally strong at the two adjacent axes, the correct axis lies midway between. B. But if the signal is stronger at one cardinal axis than at the other, then the correct axis will be found nearer the stronger signal.

RULE.—All that has to be remembered is that acceptance of the auxiliary cylinder at the axis of the plus cylinder in any position in the trial frame denies astigmatism at that axis. On the other hand, any

other response whatever shows astigmatism at or near the axis then occupied by the plus cylinder. The amount will be determined in the manner described under the heading "The Subtraction Test for Power."

REFINEMENTS

A host of modifications will suggest themselves, for example:

A. The difference between two 0.37 D. cylinders at adverse axes is 0.75 D. Between two 0.50 D. cylinders the difference is 1.00 D. These contrasts are usually large enough to be easily recognized, but higher cylinders may be used. As Lancaster suggested, persons with larger errors may not be sensitive to small differences. This holds both for the trial case cylinder and for the subtracting cylinders.

B. The ratio between trial frame and subtracting cylinders may be altered, though without much advantage as a rule.

Fig. 3.—Modified axis test. The trial frame cylinder is at a minor axis (75 degrees). Oblique subtracting cylinders are equidistant at 105 and 45 degrees.

C. The trial frame cylinder need not be confined to the cardinal axes. It may be rotated to an intermediate axis, such as 67½ degrees or 22½ degrees, A test of the four intermediate axes in addition to the test of the cardinal axes, as described, is of course more thorough but is rarely helpful. Still other positions, such as 10 degrees or 7 degrees, can be used.

D. The axis of the subtracting cylinders may, as with cross cylinders, be oblique to that of the trial frame cylinder. With the trial frame cylinder at 90, for example, the subtracting cylinders may be held at 45 and 135.

E. The subtracting cylinders need not be at right angles to each other. When the trial frame cylinder is at 90 degrees, for instance, the subtracting cylinders may work best at 120 degrees and 60 degrees.

F. The axes of the subtracting cylinders may be at unequal distances from the trial frame axis. This modification is rarely useful and complicates the interpretation.

The effect of these modifications is obvious. Those performed by rotating the trial frame cylinder to a minor axis and holding the subtracting cylinders obliquely to the trial frame cylinder and to each other, as in figure 3, are the most often used.

TEST CARD

The subtraction method is adapted for use with any ordinary test card. I still prefer the acute-angled characters, such as the ZN and the modified Maltese cross, because their sharper contrast seems to make decisions easier for the patient. An acute-angled symbol is strikingly distorted with even a slight deviation in axis. The method will, however, work well with regulation test objects. The Snellen chart is often entirely satisfactory, as are Verhoeff's circles. Highly effective is the regular astigmatic dial as recommended to me by Crisp for use with cross cylinders.

The object of bringing to attention this way of uncovering astigmatism is twofold. 1. It is a simple method suitable for routine use which requires no special lenses not found in every trial case. 2. When other methods fail, this one furnishes an additional means for disclosing an elusive cylindric error. Thus, when retinoscopic observations are contradictory, "rocking" the cylinder brings no response, use of cross cylinders gives uncertain results or results with the dial are perplexing, then the subtraction test may give a clue. That does not mean that the subtraction test is a more delicate test than those mentioned, merely that it is especially easy for some persons. There are persons for whom one of the other methods is better. There is no universal method. Every test fails sooner or later.

The customs of American ophthalmologists reflect the variability in patients. A study of the current case reports submitted to the American Board of Ophthalmology as part of the requirements for the certificate disclosed that ophthalmologists seem equally divided between those who without check prescribe cylinders from their retinoscopic findings and those who make use of cross cylinders. About a quarter employ the astigmatic dial. This is a marked improvement over a similar analysis conducted several years ago, which showed only about 5 per cent using the dial.

SUMMARY

The essence of this test lies in (1) the trial frame cylinder rotated to the cardinal axes and (2) the pair of minus cylinders at opposed axes alternated in front of it. Obviously the same mathematical end result can be arrived at in other ways. The same effect might be expected from cylinders alternated before the spherical correction, from cross

cylinders or from various spherocylindric combinations. In practice, however, some patients respond to one technic, while for others different tests are needed.

These remarks bespeak a little more allowance for the preferences of the patient in the amount of astigmatism that should be corrected, in the consideration to be given a low cylindric error and in the choice of the test to be used. No method of examination is adapted to every patient. Some patients seem resistant to all the standard technics. An additional means for estimating astigmatic errors is described. It has previously been outlined under the name subtraction method. It is rapid and easy and works well either as a routine or as a supplementary test. It requires no special lenses or apparatus.

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PRINCIPLES OF TONOMETER STANDARDIZATION

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AND
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DETROIT

The errors in tonometry arise from three principal sources. The first is entirely within the instrument, which may furnish wrong data owing to poor construction. The second involves the examiner who obtains inaccurate results from a good instrument because of faulty application or inaccurate reading. The third occurs because, although the results may be as good as possible, their quantitative interpretation is wrong owing to misconceptions of the principles involved. This paper is concerned only with the first source of tonometric errors, the apparatus itself, in its most widely used form, i. e., the Schiøtz tonometer.[1]

The accuracy demanded of any tonometer has two aspects. Priestley Smith [2] formulated the distinction with his customary insight: 1. With what degree of accuracy can one measure the impressibility of the eye? 2. With what degree of accuracy does the impressibility indicate the intraocular pressure? The kind of accuracy with which this paper is concerned is only that of the measuring of the impressibility of the eye.

If all Schiøtz tonometers were built according to the standards as given by Schiøtz himself, no ophthalmologist would need to consider calibration and standardization of his tonometer. Both procedures would have been taken care of by the manufacturer, the perfect solution of the problem thus being provided. This has been the goal of the makers of Harrington's [3] instrument.

The need for calibrating devices and adjustment of Schiøtz tonometers for general comparability of their performances was fully realized by Schiøtz [4] and has recently been stressed by Reese.[5] Two

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This investigation was supported in part by the Jennie Grogan Mendelson Memorial Fund for Ophthalmology.

1. Dr. Parker Heath suggested this study and guided its prosecution.

2. Smith, P.: Ophth. Rev. **34**:65, 1915.

3. Harrington, D. O., and Parsons, A. H.: Tonometric Standardization: Method of Increasing Accuracy of Tonometry, Arch. Ophth. **26**:859 (Nov.) 1941.

4. Schiøtz, H.: Brit. J. Ophth. **4**:201 (May) 1920.

5. Reese, A. B.: Am. J. Ophth. **25**:478 (April) 1942.

main methods have been used: A. The quantitative properties of the "unknown" tonometer are checked as to weight, radius of curvature, surface area of foot plate and plunger, etc., and are compared with those of Schiøtz' standard. B. The performance of the "unknown" tonometer on a cornea or cornea-like membrane is tested under standardized conditions and compared with the performance of a standard tonometer.

In order to appraise these methods we will first consider the influence of the parts of the tonometer on the reading.

When a tonometer is put on an eye its total weight rests on the cornea. This weight is the sum of two independent contributions: that of the foot plate assembly (including the graduated arc) and that of the plunger assembly (including the pointer and the extra weight, if used). The standard weight of the foot plate assembly is 12.0 Gm. and that of the plunger unit 5.5, 7.5 or 10.0 Gm. The weight of these parts exerts its force on a given area, namely the eye-contacting surfaces of the concave plunger and the foot plate, with their curvatures of 15.0 mm. radius. Since the plunger has no mechanical connection with the foot piece (if one disregards friction), the 12.0 Gm. of the foot plate assembly is exerted on an area of about 77.0 sq. mm., while the weight of the plunger assembly is distributed over a surface of about 7.0 sq. mm.[4] The plunger depresses the cornea. Each 0.05 mm. of its downward movement produces a 1.0 mm. movement of the pointer, i. e., a magnification of twenty. The plunger finally comes to rest when the upward pressure against the supporting corneal area equals the downward pressure.

With the exception of the "magnification" factor (which will be dealt with later) all variations in tonometer design influence the relation between weight and surface area. The area of the plunger in contact with the cornea, over which the 5.5, 7.5 or 10.0 Gm. is exerted, influences the depth of implantation. If the plunger surface of 7.0 sq. mm. exerts a force of 5.5 Gm., 1 sq. mm. of cornea sustains about 0.8 Gm. This downward pressure of 0.8 Gm. per square millimeter, or 80.0 Gm. per square centimeter, must be in equilibrium with an upward pressure of 80.0 Gm. per square centimeter, i. e., with a water column of 80 cm.

Let us assume a surface area of 6.0 sq. mm. instead of 7.0 sq. mm. The corresponding water column will be about 90 cm. If, on the other hand, the weight of the plunger assembly should be 4.5 Gm. instead of 5.5 Gm., 1 sq. mm. of the total surface of 7.0 sq. mm. would exert a force of about 0.64 Gm. The corresponding water column would be 64 cm., instead of a proper 80 cm. The smaller the weight and the surface area, the greater the relative deviation originating from the same absolute one and the more important its influence on the result.

This consideration explains why any change of the 77.0 sq. mm. surface area of the foot plate is much less serious than a change of the 7.0 sq. mm. surface area of the plunger. Less serious also is the result of an alteration in weight. The foot plate assembly bears on the cornea with a force of 0.16 Gm. per square millimeter, as compared with 5.5/7, or about 0.8 Gm. per sq. mm., in the plunger assembly. These facts were borne out in an experiment performed by Arnold and Karpow.[6] They added weights to a tonometer on an eye and first found a difference in reading (one fourth to one half of the scale unit) for a 5 Gm. increase. Their conclusion as to the irrelevancy of differences in tonometer weights is partly correct. They placed the load on the foot plate assembly and thereby demonstrated only the relative insensitivity of this part of the tonometer to changes in weight. Had the extra weight been added on the plunger assembly, very different results might have been obtained.

TABLE 1.—*Possible Relations of Weight and/or Contact Area of a Given Tonometer to Those of the Standard Tonometer*

Foot plate assembly weight and/or area	>	>	>	=	=	=	<	<	<
Plunger assembly weight and/or area...	>	=	<	>	=	<	>	=	<
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*j*

A short tabulation will provide a complete survey of all possible alternatives mentioned. The total weight of the tonometer, represented by an individual rectangle, and/or the total surface area of plunger and foot plate can be greater than (>), equal to (=) or smaller than (<) the corresponding standard. Broken down into the separate variations of the foot plate and plunger assemblies, the tabulation, shown in table 1, includes all possibilities.

This survey shows that: 1. The total weight (or area) of a given tonometer is greater than the standard in rectangle "*a*," "*b*" and "*d*," since one assembly exceeds the standard, the other being equal or also greater. 2. The total weight (or area) of a given tonometer is less than the standard in rectangle "*f*," "*h*" and "*j*," for similar reasons. 3. The most interesting situation lies in "*c*," "*e*" and "*g*." While only in "*e*" does the ideal agreement exist between the given tonometer and the standard, rectangles "*c*" and "*g*" can simulate an ideal agreement, if the variations of foot plate and plunger assemblies cancel one another, thus leaving the total weight of the tonometer unchanged. Since the significance of a variation of the plunger assembly is very different from

6. Arnold, G., and Karpow, C.: Klin. Monatsbl. f. Augenh. **71**:603, 1923.

that of a variation of the foot plate assembly, the total weight of a tonometer is a meaningless value. Unfortunately, even in case "*e*" the ideal agreement in weight does not make a tonometer more trustworthy, because of the further importance of the contact surface. Equality in weights can be rendered worthless by changes in surface areas. On the other hand, an alteration of weight can be compensated by a corresponding alteration of surface. These facts are easily seen when one reminds oneself of the possible variations of surface area, previously discussed. Such differences in surface occur if the radius of curvature of foot plate and/or plunger is changed. As in the case of weight, the effects of altering foot plate and plunger are different. The significance of the curvature of the foot plate lies in its being much flatter than the normal cornea (15.0 mm. radius versus 7.0 to 8.0 mm.). If the radius of curvature of the foot plate should be smaller than that of the cornea, the foot plate and cornea might not be in complete contact and a deflection of the pointer might be produced without a corresponding indentation of the cornea. However, since the radius of curvature of the foot plate is far in excess of that of any normal cornea, a slight deviation of its curvature will be of no detrimental influence as long as the cornea is in full contact. On the other hand, even the slightest alteration of the curvature of the plunger surface has profound influence on the effective area and, consequently, on the indentation, as Schiøtz [4] has shown.

Our general conclusion is that methods involving measurements of the tonometer or its parts are unreliable, for the evaluation of such measurements is so complicated that the methods are impractical. Besides, the physician's reasoning might go thus: Tonometers generally do not agree with the standard; exact copies of the standard tonometer are not and never have been available; none of the faults in weight or surface can be corrected; so, would not the only check of practical importance consist in the testing of the correspondence between scale reading and vertical displacement of the plunger?

Such a simple check has been suggested by Comberg.[7] He designed a series of three blocks of metal, the first representing the usual one for zero position and the second and third blocks each having a central depression allowing a downward movement of the plunger of 0.5 and 1.0 mm., as indicated on the standard instrument by ten and twenty scale units respectively. By means of these blocks, a calibration of sorts can be performed. This method reveals the actual relation between plunger movement and pointer movement, i. e., the magnification. Actual comparisons have shown [6] that tonometers which match on the test blocks may register differently on the same eye. From the foregoing

7. Comberg, W.: Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **43**:303, 1922; Klin. Monatsbl. f. Augenh. **79**:364, 1927.

discussion, it should now be clear that the depth of the corneal indentation is determined by the highly complex relations between (1) the weight of the foot plate assembly and its contacting surface and (2) the weight of the plunger assembly and its contacting surface. The three block method cannot take account of all the factors which control the recording. It is from this serious failure of all methods which rely on measuring of the static properties of a given tonometer that the need for the much more complicated measurements of the actual performance of tonometers has arisen.

Reports of attempts at dynamic calibration and standardization (i. e., with the tonometer in actual use) are scattered throughout the ophthalmologic literature. Schiøtz [4] described an artificial eye which served as a quantitatively controlled pressure chamber and had a rubber membrane for the cornea. He rejected the use of real eyes for standardizing purposes and emphasized that a standardizing apparatus was needed whose performance could always be repeated. He stated the belief that his artificial eye fulfilled this condition. Priestley Smith [2] recalibrated the Schiøtz tonometer, using human eyes. Arnold and Karpow [6] rejected rubber and leather membranes as unreliable. They declared human and pig eyes unsuitable and searched for a membrane with constant elasticity. Ultimately, they proceeded as follows: A tension was produced in a rubber membrane which would yield a reading of 2.75 with a standard 5.5 Gm. Schiøtz tonometer. On this membrane an "unknown" tonometer of the same (supposed) weight was compared with the standard. Thereafter, without a change in the tension of the membrane, comparisons were made with the 7.5 and 10.0 Gm. weights. Ferree and Rand [8] described an elaborate apparatus involving a rubber membrane on an artificial eye. Adler, Berner and Meyer [9] designed a manometer which they used with cat eyes, which they favored because of anatomic and dimensional similarity to the human eye. Friedenwald [10] has suggested that chamois or kidskin would be preferable to a rubber membrane. He expressed the opinion that any mechanical standardizing device should imitate as nearly as possible the physical characteristics of the real cornea.

For evaluation of these various devices, the principal features of the problem they involve must be outlined:

The Schiøtz chart of tonometer readings and pressures represents the average from 20 enucleated human eyes.[11] Thus, if an unknown

8. Ferree, C. E., and Rand, G.: Checking Standard for Tonometers, Arch. Ophth. **6**:689 (Nov.) 1931.

9. Adler, F. H.; Berner, G. E., and Meyer, G. P.: Report of the Subcommittee on the Standardization of Tonometers, Tr. Sect. Ophth., A. M. A., 1934, p. 321; Instrument for the Standardization of Tonometers, ibid., p. 328.

10. Friedenwald, J. S.: Am. J. Ophth. **20**:985 (Oct.) 1937.

11. Schiøtz, H.: Acta ophth. **2**:1, 1924.

tonometer should be checked against this chart, no single human eye could possibly serve; rather, at least 20 would be needed. The same statement holds true for any animal eye which might be used as a substitute: Regardless of its similarity to the human eye, no single eye would be sufficient. Furthermore, the individual variation of the animals in question must be determined before a number (of eyes) can be suggested which will yield a reliable average.

If a tonometer is to be calibrated, either a standard eye (making the use of a standard tonometer unnecessary) is required or else a standard tonometer. Thus the standardization of an unknown tonometer can be performed on a proper artificial eye without actual comparison of the "unknown" tonometer in each instance with a standard tonometer. In the construction of appliances involving artificial eyes and artificial corneas, much stress has been placed on the need for maximal accuracy in creating "intraocular" pressures and/or artificial membrane tensions.

Underlying this method is the assumption that the unknown tonometer and the standard instrument, if they agree on such an eyelike device, will also agree on an actual eye. We feel, however, that the accurate adjustment of pressures and tensions and complete reproducibility of the results, essential as they are, are problems of secondary importance. The questions of primary importance are: Does a perfect match between the standard and the unknown tonometer on a false cornea remain a match on a real one, and do the differences in reading of the standard and the unknown tonometer remain the same at all pressures regardless of the type of membrane used? These questions must be answered essentially in the negative. Arnold and Karpow [6] seem to have realized the unsatisfactory character of the situation and restricted their attention to a single point of the scale, the reading "2.75." It must be emphasized that their comparisons between standard and unknown tonometers are valid only for the membrane they used and the special conditions under which the testing was performed. Any a priori generalization from varying conditions on one kind of membrane or from constant conditions on two or more kinds of membrane is unjustified. This fact was fully realized by Friedenwald [10] when he asked for a membrane which would imitate as closely as possible the physical characteristics of the real cornea. A full explanation of the need for practical duplication of the real cornea would involve the whole theory of implantation tonometry. Only this much can be said here: The depth of indentation of any membrane covering a natural or artificial eye does not depend exclusively on the intraocular pressure but depends also on elastic forces originating in the membrane itself and modified under the influence of the tonometer. The indentation of the membrane depends on the relations of curvatures, weights and surfaces of the

plunger and foot plate in contact with the membrane. The resulting deformation in turn controls the distribution of elastic forces in the membrane. Moreover, any change in pressure will produce changes and redistribution of the elastic forces already existing. Differences in performance between the standard and the unknown tonometer which fail to show on one type of membrane or at a certain pressure range may become manifest on a membrane with different physical properties in spite of identical "intraocular" pressure, or they may reveal themselves on the same membrane when it is subjected to different pressures.

Excellent suggestions have been made, and splendid apparatus constructed, for the purpose of calibration and standardization, and yet the situation remains unsatisfactory. There is no standard natural eye, and there is not yet a standard artificial membrane with which to replace the cornea. However, a satisfactory compromise should be attainable.

In this connnection Friedenwald's suggestion (of a leathery membrane) seems the most promising. The physical properties of the membrane should be as nearly as possible those of the human cornea; i. e., the membrane should yield Schiøtz readings as close as possible to those of the Schiøtz chart. Obviously a mammalian cornea offers the highest probability of satisfying these conditions. Dimensional similarity is not the main feature to be sought—tonometric similarity is more essential. Behavior toward tonometry can be really explored only by averaging the results from such numbers of eyes as will yield smooth graphs. This procedure necessitates a standard tonometer. This standard instrument will be indispensable also in any future checking of a given tonometer on an eye of the species selected for standardizing, since no individual eye can be expected to coincide with the average eye. A transference of the comparison between a standard and an unknown tonometer from a subhuman eye to a human one is justified only if the tonometric readings represent the same dependence on intraocular pressure, in spite of some difference in absolute values. In other words, the same mathematical function, symbolized by the hyperbolic curve on the chart, should describe the relationship between intraocular pressure and impressibility for the two corneas, their differences being expressed by certain constants.

We decided on the pig eye for a methodical investigation of tonometric properties. The result of testing 30 enucleated eyes with a manometer based on the Adler-Berner-Meyer instrument [9] was perfectly satisfactory, despite the pessimistic implications of Arnold and Karpow's [6] discussion of this animal. Figure 1 is organized like the customary Schiøtz chart. The three solid curves represent the pig eye and the dotted curves the Schiøtz standard human eye. A comparison

of the two sets shows that the curves for the pig eye belong to the same type as those for the human eye, namely, the hyperbola, thus indicating the same type of relationship between impressibility of the cornea and tonometric reading. For the same reading and weight, the pressure is higher in the pig eye than in the human eye. For a weight of 5.5 Gm. the curves for the pig eye and for the human eye run practically parallel between readings of 2 and 8, the constant difference throughout this range being a matter of about 5 mm. of mercury. These data indicate the possibilities and limitations of the pig eye as a test object for standardization. The desired tonometric similarity to the human eye is present. For a weight of 5.5 Gm. and the scale interval between 2 and

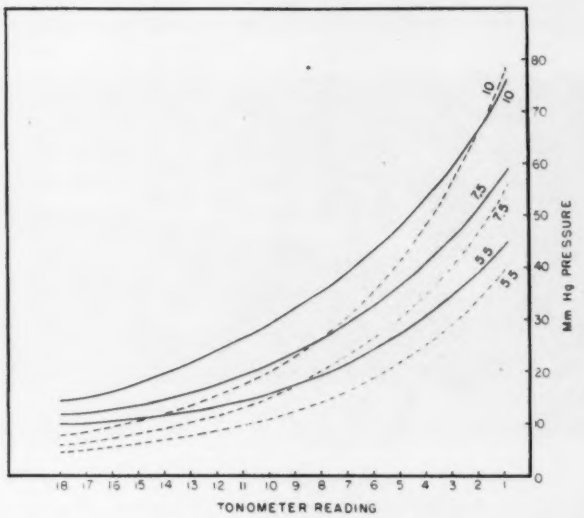

Fig. 1.—Schiøtz tonometer readings and actual intraocular pressures for 30 pig eyes (unbroken lines), compared with similar data (after Schiøtz [11]) for 20 human eyes (dotted lines). Each curve is labeled with the weight (in grams) with which it was determined.

8, the pig eye and the human eye exhibit the same relationship of pressure and reading. The only difference is the vertical displacement of the curve for the pig eye. Hence we conclude that for this particular weight and range, a difference in reading between standard and unknown tonometers, as revealed on a pig eye, is most likely to be duplicated on a human eye. The restriction to the scale range from 2 to 8 is necessitated, furthermore, by the known fact that the Schiøtz data decrease in reliability beyond these points.

So far, the testing of tonometers appears to be settled for a 5.5 Gm. weight. We feel, however, that the problem has not been solved for

the 7.5 and 10.0 Gm. weights. With any given combination of tonometer and eye, the relative positions of the three curves are determined by the ratio 5.5 : 7.5 : 10.0. In an unknown tonometer, the designated value "5.5" of the plunger assembly is actually doubtful, thus rendering dubious the existence of a 5.5 : 7.5 : 10.0 ratio. Therefore, the relative positions of graphs for the pig eye and the human eye for 7.5 and 10.0 Gm., such as are shown in the chart, could not be computed from the curve obtained for 5.5 Gm. with an unknown tonometer. Nor would a direct comparison between the standard and the unknown tonometer on a pig eye with 7.5 and 10.0 Gm. weights justify a construction of corresponding curves for the human eye, since the respective curves do not run parallel in the range of reliable readings.

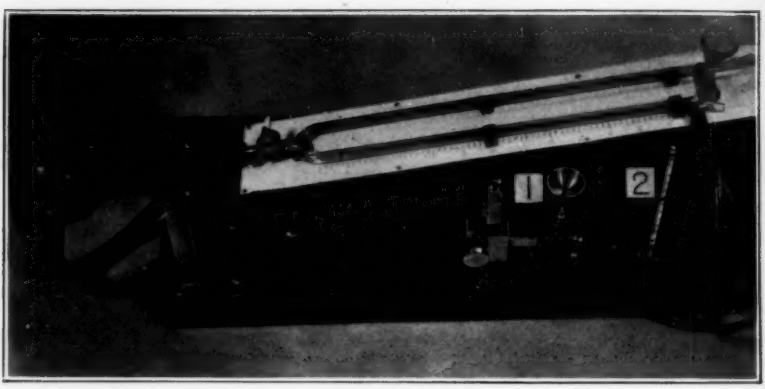

Fig. 2.—Manometer for standardization of tonometers. *1*, Luer-Lok needle and cup; *2*, device for determining the height of the cornea. The figures (in millimeters) along the vertical scale correspond to others on the manometer board.

PROCEDURE USED IN TONOMETRIC TESTING OF THE PIG EYE

Apparatus.—A manometer was built based on the "apparatus for standardization of tonometers" [9] with two modifications (fig. 2):

1. Instead of the oval plate to be introduced through a scleral slit, and the washer and nut for tight occlusion, there was a short no. 13 Luer-Lok needle to be inserted axially through the optic nerve into the vitreous and tightly ligated with silk. Aside from the Luer-Lok feature, the connection with the tonometer was the same as that described by Adler, Berner and Meyer, so that two advantages were achieved: (*a*) in case of obstruction the eye could be removed with the needle *in situ* and the communication restored, and (*b*) when eyes other than pig eyes were being used, the Luer-Lok socket would take any gage of needle.

2. The eye rested in a hemispherical metal cup which slid vertically on the needle and could be fixed at any desired height. The space between the eye and the wall of the cup was filled with liquid agar at 40 C., which when gelated prevented any movement.

Tonometer.—The particular Schiøtz tonometer used was a German (Wocher) model (serial no. 1801) and was applied by hand. No claim can be made that this instrument is a true "standard" Schiøtz tonometer, but of course it served as well as any for the demonstration of the principles of standardization.

Eye.—Pig eyes have several advantages. They are easily available in sufficient number. Abattoir animals have an average age of 7 to 8 months (thus providing a uniformity of age which is impossible with cats or dogs). The routine procedure of scalding the carcasses in water at 70 C. does not affect the usefulness of the eye as a tonometric membrane. We have not, of course, charted the tonometric properties of the normal pig eye in vivo.

The eyes were used within one to two hours after enucleation. The cornea was kept moist with physiologic solution of sodium chloride or tap water (no difference being found). The fluid siphon between the mercury in the manometer and the vitreous was either physiologic solution of sodium chloride or tap water, which, too, introduced no differences within the forty-five minutes required for a full set of readings.

TABLE 2.—*Data on Which the Solid Curves in Figure 1 Are Based*

Scale interval.....		0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16	16-18
Tonometric reading	With 5.5 Gm. wt.	0.8	2.7	4.6	6.7	8.6	10.4	11.8	14.7	17.6
	With 7.5 Gm. wt.	0.7	2.7	4.6	6.9	8.5	10.8	12.5	14.6	17.0
	With 10.0 Gm. wt.	0.8	2.6	4.8	6.7	8.5	10.5	12.7	14.6	17.0
Manometric pressure, mm. of mercury *	With 5.5 Gm. wt.	45.5	35.5	29.0	22.5	18.5	15.0	13.5	11.5	11.5
	With 7.5 Gm. wt.	59.5	47.5	37.5	30.5	24.5	20.0	16.0	14.5	13.5
	With 10.0 Gm. wt.	76.0	61.0	49.5	40.5	33.5	28.0	21.5	19.5	16.5
Number of determinations /interval	With 5.5 Gm. wt.	37	31	16	18	18	10	10	4	3
	With 7.5 Gm. wt.	38	38	25	20	17	14	18	6	7
	With 10.0 Gm. wt.	47	43	30	26	24	17	13	14	7

* To the nearest half-millimeter; the accuracy of the manometric readings was ± 0.5 mm. of mercury.

Readings.—Instead of Schiøtz'[11] five readings for each weight and at each pressure point, only three readings were taken, since the reliability of the preparation decreases steadily. For the same reason, we deviated from Schiøtz' procedure in that we did not produce a series of identical pressures with each of the three weights. Instead, from a minimal pressure which would still record on the scale, we proceeded in steps of about 10 mm. of mercury with each weight, starting with 5.5 Gm. Since a slight leakage is unavoidable, we read the pressure from the manometer scale before and after each set of three readings and recorded the average of the three readings and the average of the before and after pressure. Otherwise, the procedure was the same as that described by Adler, Berner and Meyer.[9]

Computation of the Results.—The scale readings were divided into intervals of two units. For each interval the products of the pressure values and their respective frequencies of occurrence (with a given weight) were summated and divided by the number of determinations, thus yielding the average pressure ordinate of the interval in question. For each interval and weight, also, the products of all scale readings and their frequencies of occurrence were summated and divided by the number of determinations, thus yielding the average scale-reading abscissa of each interval. This procedure furnished the three series of points (one for each weight) through which the dotted curves of figure 2 were drawn. The data are summarized in table 2.

The following procedure is suggested for relating the performance of an unknown to a standard tonometer:

1. A fresh pig eye should be used.

2. Alternating readings should be taken with a standard and with the unknown tonometer with a weight of 5.5 Gm. and with pressures of 15 to 40 mm. of mercury in steps of about 5 mm. If the readings with the standard tonometer when compared with the 5.5 Gm. curve for the human eye indicate a definite departure from parallelism, the pig eye should be discarded and another substituted.

3. Graphs should be plotted for both the standard and the unknown tonometer of the readings versus pressure on the pig eye, to reveal any corrections which must be added or subtracted from any pressure reading of the unknown tonometer for any scale reading between 2 and 8 on the Schiøtz standard chart for the human eye.

4. If the pressure of the human eye to be measured is so high that it cannot be recorded between 2 and 8 on a Schiøtz tonometer of 5.5 Gm. weight, then the operator must proceed to use the unknown tonometer entirely at his own risk and with no assurance that it, in connection with the Schiøtz chart, will tell him the truth.

CONCLUSIONS

The ideal solution to the problem of standardization is to eliminate it by persuading manufacturers to produce only absolutely uniform instruments. If this proves impossible, then the method herein outlined, though far from perfect, demonstrates the course which investigation should follow in the future. Since a standardization for all weights and for the whole scale is perhaps impossible with any one animal eye, an artificial membrane must be developed whose tonometric properties will exactly duplicate those of the average human eye.

DEGENERATION AND REPAIR OF THE RAT RETINA IN AVITAMINOSIS A

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Although night blindness and various other ocular disturbances have for centuries been associated with a dietary deficiency of the body, it is only within recent years, through the work of Fridericia and Holm,[1] Tansley[2] and others, that vitamin A deficiency has been identified as the specific cause of these visual defects. Still more recently the investigations of Wald[3] have revealed that vitamin A is directly concerned with the visual process in that it is the precursor of visual purple as well as a product of its decomposition. It has been shown also, in experimental studies, that adult human subjects (Wald, Jehgers and Arminio,[4] Wald and Steven,[5] Booher, Callison and Hewston[6] and Steven and Wald[7]) and infants (Lewis and Haig[8]) kept on a diet low in vitamin A until a certain degree of night blindness was exhibited recovered normal vision with startling rapidity on the administration of vitamin A. Likewise, large daily doses of vitamin A were found by Haig, Hecht and Patek[9] to cure night blindness in persons with alcoholic cirrhosis of the liver. These findings might be taken as an indication that night blind-

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3. Wald, G.: Vitamin A in Eye Tissues, J. Gen. Physiol. **18**:905-915, 1935; Carotenoids and Visual Cycle, ibid. **19**:351-371, 1935; Pigments of the Retina: I. The Bullfrog, ibid. **19**:781-795, 1936.

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6. Booher, L. E.; Callison, E. C., and Hewston, E. M.: An Experimental Determination of the Minimum Vitamin Requirements of Normal Adults, J. Nutrition **17**:317-331, 1939.

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9. Haig, C.; Hecht, S., and Patek, A. J.: Vitamin A and Rod-Cone Dark Adaptation in Cirrhosis of the Liver, Science **87**:534-536, 1938.

ness is a purely functional disorder due to the simple lack of a substance essential to the visual processes, a disorder which might be cured by supplying, in adequate amounts, the missing vitamin A.

However, a further review of studies on human subjects and experimental animals reveals that normal vision is not always immediately restored when adequate amounts of vitamin A are added to the diet. For example, Hecht and Mandelbaum [10] and MacDonald and Adler [11] have found that, although partial recovery of vision occurred in some persons (with experimentally induced avitaminosis A) after a single dose of vitamin A, permanent, complete recovery was slow, weeks and in some cases even months of a normal diet, with or without supplementary vitamin A, being required to effect a complete return to normal vision. Furthermore, Moore, Huffman and Duncan,[12] Hart and Guilbert [13] and Moore [14] have reported instances in sheep and cattle of dietary night blindness which was permanent although adequate amounts of vitamin A were administered for months in an attempt to cure it. These instances—particularly the ones in which the condition responded slowly if at all to continued vitamin A replacement therapy—seem to indicate that something more than the simple lack of a substance (vitamin A) essential to the formation of visual purple is involved in the production of dietary night blindness.

That vitamin A deficiency does indeed produce more than a mere functional disarrangement in the retina is shown by the work of Tansley [15] and by my [16] work. Tansley, in studies of the retinas of vitamin A–deficient rats and dogs, found certain changes in the histologic appearance of the visual cells; namely, abnormal staining of the outer segments of the rods, thinning of the junction between the inner

10. Hecht, S., and Mandelbaum, J.: Rod-Cone Dark Adaptation and Vitamin A. Science **88**:219-221, 1938; The Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1910-1916 (May 13) 1939; Dark Adaptation in Vitamin A Deficiency, Am. J. Physiol. **130**:651-664, 1940.

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13. Hart, G. H., and Guilbert, H. R.: Symptomatology of Vitamin A Deficiency in Domestic Animals, J. Am. Vet. M. A. **91**:193-200, 1937.

14. Moore, L. A.: Relationships Between Carotene, Blindness Due to Constriction of the Optic Nerve, Papillary Edema and Nyctalopia in Calves, J. Nutrition **17**:443-459, 1939.

15. Tansley, K.: Factors Affecting the Development and Regeneration of Visual Purple in the Mammalian Retina, Proc. Roy. Soc., London, s.B **114**:79-103, 1933; The Effect of Vitamin A Deficiency on the Development of the Retina and on the First Appearance of Visual Purple, Biochem. J. **30**:839-844, 1936.

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and the outer segments and in some areas complete degeneration of the outer segments of the rods. My observations on the retinas of rats suffering from what was termed "moderate avitaminosis A" substantiated Tansley's findings. Furthermore, I also found that the retinas of rats exhibiting signs of severe vitamin A deficiency showed more marked degeneration, which apparently was progressive, beginning with the outer segments of the rods and involving in order the inner segments of the rods, the external limiting membrane, the outer nuclear layer, the epithelial pigment layer, the outer molecular layer and the inner nuclear layer. The inner molecular layer, the ganglion cell layer and the nerve fiber layer apparently remained intact. It seems apparent from these observations that avitaminosis A produces a dysfunction of the rods not only through the removal of a substance essential to the formation of visual purple but through an actual degeneration of the rods and in cases of severe involvement of all the layers of the retina sclerad to the inner molecular layer.

The finding of structural changes in the retinas of vitamin A–deficient animals—changes ranging all the way from a mere change in staining properties of the outer segments of the rods to degeneration of several layers of the retina in instances of the most severe involvement—may offer an explanation for the great variety of results obtained by investigators studying dark adaptation in human beings recovering from avitaminosis A. In a previous paper I [16] concluded tentatively that degeneration involving only the outer segments of the rods may not be irreparable but may, in fact, be repaired in a relatively short time by the administration of vitamin A and that degeneration involving several layers of the retina probably is incapable of repair. However, as stated at that time, these conclusions cannot be considered as highly significant for two reasons: (1) they were based on a small number (4) of recoveries and (2) no attempt was made to determine the condition of the retina at the time the animal was placed on the recovery diet, so that the amount of repair which occurred in the retina during recovery could not be definitely known but only surmised.

The present study was undertaken, therefore, with the idea of obtaining a better knowledge and more complete understanding of the structural changes taking place in the retina during recovery from avitaminosis A. In an effort to overcome the objections to the earlier study, a large number of experimental animals was used and one eye was enucleated when the animal exhibited the proper symptoms of avitaminosis A and was studied histologically to determine how much degeneration had occurred in the retina before the animal was placed on the recovery diet; the second eye was excised after the animal had been permitted to recover for a given length of time on an adequate diet and was compared with the first (control) eye to determine what repair, if any, had occurred during the time on the recovery diet.

EXPERIMENTS

Three strains of rats were used in this study: (1) rats of the Long-Evans strain, from the animal colony of the department of anatomy, Columbia University College of Physicians and Surgeons; (2) rats of the Sherman strain, from the department of animal care, Columbia University College of Physicians and Surgeons, and (3) rats of the Wistar strain, from the animal colony of the New York Psychiatric Institute. Three series of experiments were carried out.

Series 1.—Nine litters of 23 day rats (62 rats) were obtained from the department of anatomy stock (Long-Evans strain). These rats, which had been suckled by mothers fed the regular stock diet, [17] were weaned on the following diets: A male and a female from each litter were placed on an adequate diet [18] to serve as control animals, and the remaining 44 rats, the experimental group, were placed on a vitamin A–free diet.[18] The control animals were given doses of cod liver oil three times a week, and both the control and the experimental animals were given two supplementary doses of dried yeast per week.[19]

Although early symptoms of vitamin A deficiency, xerophthalmia and cessation of gain in weight, do not usually occur until rats have been on the vitamin A–free

17. Stock diet fed to the Long-Evans and Sherman strain rats:

	Percentage
Ground yellow corn	15.0
Ground whole wheat	15.0
Ground hulless oats	15.0
Ground whole barley	15.0
Soy bean meal	15.0
Meat scraps	10.0
Whole milk powder	5.0
Skim milk powder	5.0
Ground alfalfa meal	2.0
Sodium chloride	2.0
Calcium carbonate	0.5
Lettuce twice weekly	

18. The diets used in this study were made up as follows:

Adequate Diet for Control Animals	Percentage	*Vitamin A—Free Diet*	Percentage
Casein (washed)	18	Casein (Harris vitamin free)	18
Corn starch	49	Corn starch	49
Crisco	10	Crisco	19
Butter fat	9	Dried yeast (irradiated and nonirradiated)	10
Dried yeast (irradiated and nonirradiated)	10	Salt mixture (Osborne and Mendel)	4
Salt mixture (Osborne and Mendel)	4		

19. Standard Brands, Inc., supplied the yeast used in these experiments and E. R. Squibb & Sons the cod liver oil used to supplement the diets of the control and the recovery animals.

diet for five to six weeks (Aberle[20] and others), all but 6 of the rats in this series exhibited xerophthalmia and a loss of weight between the fifteenth and the thirtieth day of the experiment. Furthermore, within six to ten days after the onset of these early signs of avitaminosis A, all these animals had one or more symptoms of acute and severe vitamin A deficiency. Four animals died of pneumonia, 13 had corneal ulcers (3 with hypopyon) within a few days after the first sign of xerophthalmia and 8 exhibited severe xerosis conjunctivae with large amounts of crusty material packed between the eyelids and the bulb.

The 3 animals with hypopyon were killed, because it was believed that this condition might lead to complicating secondary effects on the retina which would be confused with the effects of vitamin A deficiency per se. All except 2 of the remaining animals exhibited severe xerophthalmia or corneal ulcers or appeared to be practically moribund from other effects of the vitamin A deficiency by the forty-second day of the experiment. One eye of each of these animals was enucleated during ether anesthesia and fixed in modified Held's solution. After the enucleation, the animal was placed on an adequate diet supplemented with cod liver oil. Four of the animals operated on were killed after having been maintained on the adequate diet for seven days, 3 were killed after one, two three, four, five, seven, ten, fourteen, twenty-one, thirty, sixty and ninety days, and the second eye was excised and fixed for comparison with the eye previously removed at operation.

Histologic study of the retinas of these animals revealed none of the lesions which I[16] observed previously in a group of vitamin A–deficient rats of the Wistar strain. Therefore, two additional series of experiments were carried out to determine whether the early appearance of symptoms due to deficiency and the failure of retinal lesions to develop were due (1) to a difference in strain or (2) to the diet on which the rats had been maintained prior to the beginning of the experiment.

Series 2.—Three litters of 23 day rats of the Long-Evans strain (20 rats) and four litters of 23 day rats of the Sherman strain (22 rats) were obtained. These animals, like those of series 1, had been suckled by mothers fed the stock diet,[17] and they were weaned on the diets described previously, 1 member of each litter being placed on the adequate diet to serve as a control and the remainder (18 of each strain) being placed on the vitamin A–free diet.[17]

As in series 1, the first signs of avitaminosis A appeared earlier than was to be expected in rats of either the Long-Evans or the Sherman strain. Xerophthalmia was exhibited in rats of each strain as early as the seventeenth day of the experiment, and it was present in all but 2 of the rats by the thirty-second day. Likewise, animals of each strain showed loss of weight as early as the twenty-fifth day, and all but 6 were losing weight by the fortieth day.

It was believed that the rats in series 1 failed to show the expected retinal lesions because they had not been maintained on the vitamin A–free diet long enough for the changes characteristic of a long-continued vitamin A deficiency to take place. Therefore, in this series a rat was not placed on a recovery diet until it was evident that it could not survive longer on the experimental diet or until the condition of the cornea was such that perforation, with its subsequent complications, seemed imminent.

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20. Aberle, S. B. D.: Neurological Disturbances in Rats Reared on Diets Deficient in Vitamin A, J. Nutrition **7**:445-461, 1934.

As might be expected, the mortality rate in this series was more than double that in series 1, because many of the rats were kept on the vitamin A–free diet until irreparable, fatal effects of the deficiency had developed. Thus, 9 of the 36 animals (4 of the Long-Evans and 5 of the Sherman strain) died before one eye had been enucleated, and 7 rats were killed one to fourteen days after being placed on the adequate diet, when it became evident that death, due to severe pulmonary or renal involvement, was imminent.

In this series, the eyelids and corneas of rats showing severe xerophthalmia were cleansed once or twice daily with liquid petrolatum and treated with metaphen ophthalmic ointment.[21] The treatment appeared to be efficacious, since no serious corneal lesions occurred in the series.

Seventeen of the rats in this series were maintained on the vitamin A–free diet for eight to nine weeks before the effects of the deficiency became so severe that is was necessary to place them on the recovery diet. At that time, one eye was enucleated and fixed, in the manner described previously, and the animals were permitted to recover for various periods of time (one, three, four, ten, fourteen, twenty-eight, forty-five, fifty, fifty-five, sixty-five, seventy, eighty and ninety days) before the second eye was enucleated and fixed.

As will be seen hereafter in the section on "Histologic Observations," the animals in this series showed retinal lesions similar to those described previously by me. Thus it appears that such lesions failed to occur in the first series because, as suggested earlier, the rats were not kept on the vitamin A–free diet for a sufficient length of time. Furthermore, the almost identical reaction of the Long-Evans and the Sherman strain of rats to the vitamin A–deficient diet—with an early onset of deficiency symptoms and an early appearance of signs usually regarded as "late" manifestations of avitaminosis A—indicated that this reaction probably was due to the diet on which the rats had been maintained prior to the experiment rather than to the difference in strain. Therefore, a third series of experiments was carried out to check this probability.

Series 3.—In this series three strains of rats were used, Long-Evans, Sherman and Wistar, obtained from the sources mentioned at the beginning of this section. Female rats, each with her litter of 12 day old offspring, were fed the adequate diet[18] and were given in addition daily doses of cod liver oil and supplementary portions of dried yeast thrice weekly. Thus, the rats used in this series were suckled for the ten days prior to weaning by mothers given more than adequate amounts of vitamins A, B, G and D. When the young rats were 23 days old, 1 of each litter was placed on the adequate diet, and the remainder were weaned on the vitamin A–free diet. In all there were 4 control animals and 35[22] (8 of the Long-Evans strain, 8 of the Sherman strain and 19 of the Wistar strain) experimental animals.

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21. It should be noted here that only 2 instances of corneal ulcer were encountered in this series, as compared with 13 in series 1—additional evidence as to the efficacy of the treatment with liquid petrolatum and metaphen ointment.

22. Four of the Sherman rats were accidentally discarded shortly after the beginning of the experiment; therefore, for all practical purposes, this series consisted of 31 experimental animals.

All except 2 of the animals in this series manifested signs of vitamin A deficiency considerably later than those of series 1 and 2. Xerophthalmia made its appearance in 21 of the rats between the thirty-fifth and the forty-fifth day after they were placed on the vitamin A–free diet and in 9 animals between the forty-fifth and the fifty-sixth day. Furthermore, none of these rats showed cessation of growth until the thirty-second day, and 8 of them continued to gain in weight until the forty-fourth day of the experiment. The cessation of growth was followed by a period, varying from fifteen to sixty days for different animals, during which the weight remained at a more or less constant level. This "plateauing" of the weight curve was succeeded in most cases by a sudden loss of weight and the appearance of the more acute symptoms characteristic of the late stages of vitamin A deficiency (severe xerophthalmia, paralysis of the hindlegs, diarrhea and marked signs of pulmonary and renal involvement). Although all the animals in the group finally had severe xerophthalmia, corneal ulcers occurred in only 2.

As in series 2, the animals were kept on the vitamin A–free diet until they appeared to be moribund, then one eye was enucleated and fixed. The animals operated on were permitted to recover for various periods before the second eye was excised and fixed. As might be expected, the mortality rate was fairly high: 9 rats died before an eye had been enucleated, and 1 died as the result of a postoperative hemorrhage.

The remaining 21 rats were placed on the recovery diet after the enucleation of one eye. Twelve of these were killed between the first and the twenty-eighth day after operation, when it became evident that they were unable to survive any longer. Three of the other 9 rats in this group were killed after twelve weeks on the recovery diet, 3 after fourteen weeks and 3 after eighteen weeks. Their eyes were excised and fixed for comparison with the eyes removed earlier in the experiment.

The lenses of the fixed eyes were removed in 95 per cent alcohol, and the bulbs were embedded in paraffin and sectioned serially at 6 or 8 microns in either a mediolateral or a dorsoventral plane. In all but 7 instances, sections from the "deficient" and the "recovery" eye [23] were mounted on the same slide so that the two eyes could be stained as uniformly as possible. Most of the sections were stained with iron hematoxylin and erythrosin, but selected sections from each eye were stained with a modification of Mallory's connective tissue stain (McClung [24]), and still others with either azure II or cresyl violet.

SELECTION OF SPECIMENS

If one considers the period of vitamin A deficiency to which the animals in each of the three series of experiments were subjected, it is apparent that the animals of the three series fall into two groups:

1. The animals of series 1. These animals endured a relatively short period of avitaminosis A, because they were placed on the recovery diet as soon as the symptoms of acute, severe vitamin A deficiency were

23. Throughout the remainder of the paper, the eye enucleated before the animal was placed on a recovery, or adequate, diet will be referred to as the "deficient" eye, and the second eye, excised after a given period with the animal on the adequate diet, will be designated as the "recovery" eye.

24. McClung, C. E.: Handbook of Microscopical Technique for Workers in Animal and Plant Tissues, ed. 2, New York, Paul B. Hoeber, Inc., 1937, pp. 405-406.

manifested (between the fourth and the sixth week after the beginning of the experiment).

2. The animals of series 2 and 3. Although the animals of series 2 exhibited acute symptoms of vitamin A deficiency much earlier than those of series 3, the animals of both series were kept on the vitamin A–free diet as long as was practicable after the onset of signs of acute deficiency. Thus, the rats of series 1 and 2 endured a long period of avitaminosis A before they were placed on the adequate diet (seven to thirteen weeks from the beginning of the experiment).

Furthermore, study of the specimens has revealed that this grouping is the most convenient one to use in describing the histologic observations.

HISTOLOGIC OBSERVATIONS

Group 1.—The retinas of 30 experimental animals from this group were studied histologically. In each instance the "deficient" eye, enucleated before the animal was placed on the adequate diet, was compared with the "recovery" eye, removed after the animal had been adequately fed for a given period of time.

None of the "deficient" retinas of this group exhibited the degenerative changes described by me in 1939 as characteristic of avitaminosis A. In no instance did the retina show anything more than a general edema. In every instance the visual cells, which in my earlier study were the first to undergo degeneration, presented a perfectly normal appearance. As might be expected from the foregoing remarks, the "recovery" eyes of these animals likewise were normal in every respect.

It appears, therefore, that vitamin A deficiency of an acute, severe type—but of short duration—produces no structural changes in the retina.

Group 2.—Each of the 39 retinas in this group showed degenerative changes similar to those found previously by me in a group of vitamin A–deficient rats. Although all the rats in the present group were suffering from approximately the same degree of vitamin A deficiency when one eye was enucleated, the retinas of the "deficient" eyes by no means exhibit the same degree of degeneration. Structural changes ranging all the way from very early stages of degeneration, involving only the visual cell layer of the retina, to advanced stages, involving from two to four layers of the retina, were observed.

All these retinas showed pronounced engorgement of the retinal and choroidal blood vessels and a general edema which was particularly marked in and around the optic nerve.

In 18 of the eyes, early degenerative changes involving mainly the visual cell layer were observed. These changes were identical with those described by me in 1939 as "changes resulting from moderate vitamin A deficiency." The central regions of the retinas showed the greatest variation from the normal. Here, the outer segments of the rods failed to take the dark blue or black hematoxylin stain characteristic of the normal outer segment (fig. 1 *A*) and appeared as grayish or pink, shrunken cylindric envelopes (fig. 1 *B*). The change in staining reaction was also well shown in the sections stained with Mallory stain, in which the normal outer segments of the rods were colored bright orange but in which degenerating cells stained faintly blue or not at all. The outer segments also

appeared thinner than normal—especially at their junction with the inner segments. Complete fracture of the rods at the junction of the inner and the outer segments was observed frequently. The inner segments in these retinas were shorter than normal (compare figures 1 *A* and 1 *B*) and had a swollen, glassy appearance. The external limiting membrane in most places presented a wavy, irregular contour, in contrast to its normal sharply defined, straight course. The pigmented epithelial cells appeared normal in most places, but in areas showing the most marked changes in the visual cells, they occasionally appeared as swollen, spherical cells with pyknotic nuclei and with many fine, fatty-appearing droplets filling the cytoplasm.

The peripheral regions of the retinas exhibited less change. In some retinas, the visual cells of the peripheral portion appeared normal; in others, the rods seemed to have suffered only slightly less damage than those more centrally situated. Figure 1 *E* illustrates the latter type of retina. Here the outer segments of the rods are more tenuous than normal but are not extremely thin at the junction with the inner segments. They appear pale and shrunken because of the extreme sparsity of the dark-staining material in them.

A study of the eyes removed from the same rats after certain periods of adequate feeding revealed that the changes described are not irreparable. Figure 1 *C* shows a section from the fundus of an eye removed from an animal which had been given cod liver oil and fed adequately for the twenty-four hours immediately following enucleation of the eye illustrated in figure 1 *B*. Although the recovery period was extremely brief, the visual cells presented an almost normal appearance. Most of the outer segments of the rods were of normal thickness and were fairly well filled with a dark-staining material arranged in the form of small disks. Only a few of the outer segments remained pale-staining and tenuous. The inner segments of the rods still were shorter than normal, but they were well defined and normally stained. The unevenness of the external limiting membrane and the slight irregularity of the outer nuclear layer, which remained, were undoubtedly due to the edematous condition of the tissue.

The retinas of animals which had been fed adequately for four and ten days exhibited perfectly normal-appearing visual cells, but engorgement of the retinal and choroidal blood vessels and edema of the retina generally were still present. The retinas enucleated after twenty-one to ninety days of recovery appeared to be completely restored to the normal condition. Figure 1 *D* illustrates a section of the peripheral portion of a "recovery" retina from an animal fed adequately for twenty-eight days after enucleation of the "deficient" eye shown in figure 1 *E*. This retina showed no abnormalities except that the number of visual cells may have been somewhat reduced. (At first glance, the rods in this section appeared to be somewhat shorter than normal, but micrometric measurements revealed that they were of the same size as those in corresponding regions of retinas from normal control animals.) In fact, the only variation from the normal noted in this eye and in other eyes after twenty-one to ninety days of recovery was an increase in the amount of connective tissue in the choriocapillaris; this observation agrees with the observations of Smith, Yudkin, Kriss and Zimmermann.[25]

Although many of the remaining 21 retinas in this group exhibited, in their peripheral regions, no more damage than that already described, all of them showed areas in which the visual cell layer and two or three of the inner layers had degenerated. The extreme periphery in 13 showed changes in the visual cells similar to those described in the preceding pages, but as the more central portions

25. Smith, A. H.; Yudkin, A. M.; Kriss, M., and Zimmermann, H. M.: Vitamin A Content of Retinal and Choroidal Tissue, J. Biol. Chem. **92**:92-93, 1931.

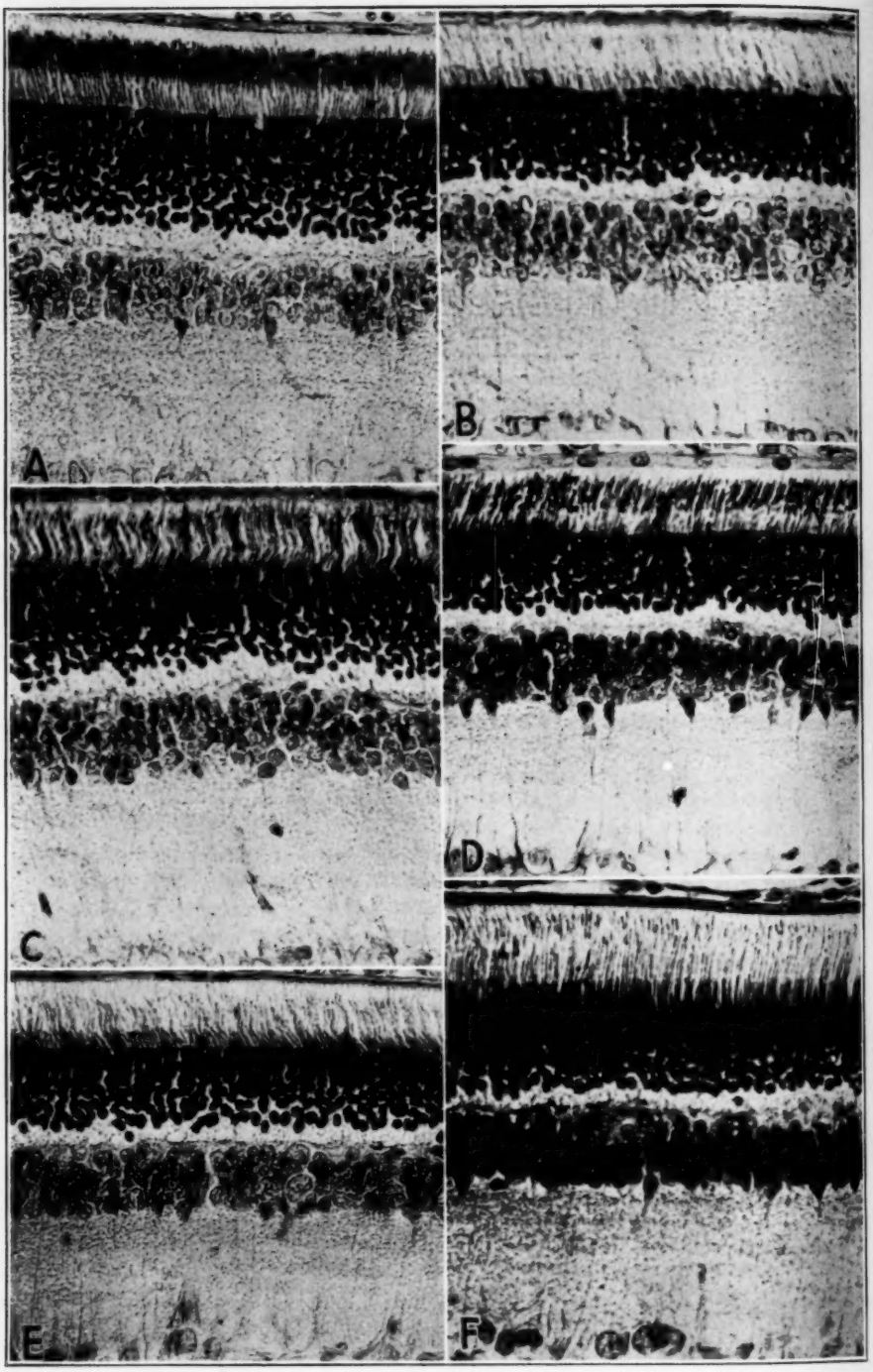

Figure 1

(See legend on opposite page)

of the retina were approached, further changes were noted. There, areas were seen in which the outer segments of the rods had completely degenerated and only the degenerating inner segments remained (fig. 2 *A*). In such places, the external limiting membrane had disappeared, and the nuclei of the outer nuclear layer were rather widely separated from each other, giving this layer an uneven, disorderly appearance. Many of these nuclei were degenerating. Still more centrally, the visual cells had completely disappeared, the outer nuclear layer was reduced to two or three rows of nuclei and the outer molecular layer was greatly diminished (fig. 2 *C*). Nissl stains revealed only a few degenerating bipolar cells and no changes in the ganglion cells. The epithelial pigment layer was invariably detached from the retina proper in all such regions. Its cells appeared normal throughout the greater part of the retina, but occasionally two or three large, bloated, spherical cells, which appeared to be desquamated pigmented epithelial cells, might be seen in regions containing large masses of degenerating visual cells. These invariably appeared unhealthy, with dark-staining, pyknotic-appearing nuclei and swollen, pale-staining cytoplasm filled with many small, shiny droplets. It may be that such cells are phagocytic, as Krückmann [26] reported, but they were not frequently encountered and no more than two or three were ever found in a given region.

Eight other eyes in this subgroup exhibited areas, throughout the retina, in which only early changes in the visual cells were observed but in which, inter-

26. Krückmann, E.: Die pathologischen Veränderungen der retinalen Pigmentepithelzellen, Arch. f. Ophth. **48**:237, 1899.

Explanation of Figure 1

Retinas from normal rats, vitamin A–deficient rats and rats which had received a recovery diet for various periods (magnification in figures 1 and 2 × 400). *A*, section from the fundus of a normal rat retina. *B*, section through the fundus of a rat suffering from severe long-continued avitaminosis A. Note especially the pale-staining outer segments of rods and the thinning of these segments at their junction with the inner segments. Compare with *A* and *C*. *C*, section through the fundus of the "recovery" retina from the animal whose "deficient" retina is illustrated in *B*. The animal had been given cod liver oil and fed adequately for twenty-four hours after removal of the "deficient" retina. The rods here are almost normally stained, and many of them are of normal thickness. *D*, section through the peripheral portion of the retina from an animal which had been adequately fed for twenty-eight days after having had severe avitaminosis A. This retina is practically normal in all respects. Compare with *E*, which shows a section from the peripheral region of the "deficient" retina from the same animal. *E*, section through the periphery of the "deficient" retina of an animal suffering from severe avitaminosis A. Note that the rods in this section have suffered somewhat less damage than those shown in *B*. Compare with *D*, which shows the "recovery" retina of this animal, noting the practically complete restoration to the normal condition. *F*, section through the periphery of an eighteen week "recovery" retina. The corresponding region from the "deficient" eye of the same animal is shown in figure 2 *A*. Note the remarkable degree of repair shown by the rods and the normal, regular appearance of the outer nuclear layer, as compared with those of the "deficient" retinas. The chief abnormalities are relative sparsity of the visual cells; abnormally long, slender outer segments of the rods and lighter than normal staining of the outer segments.

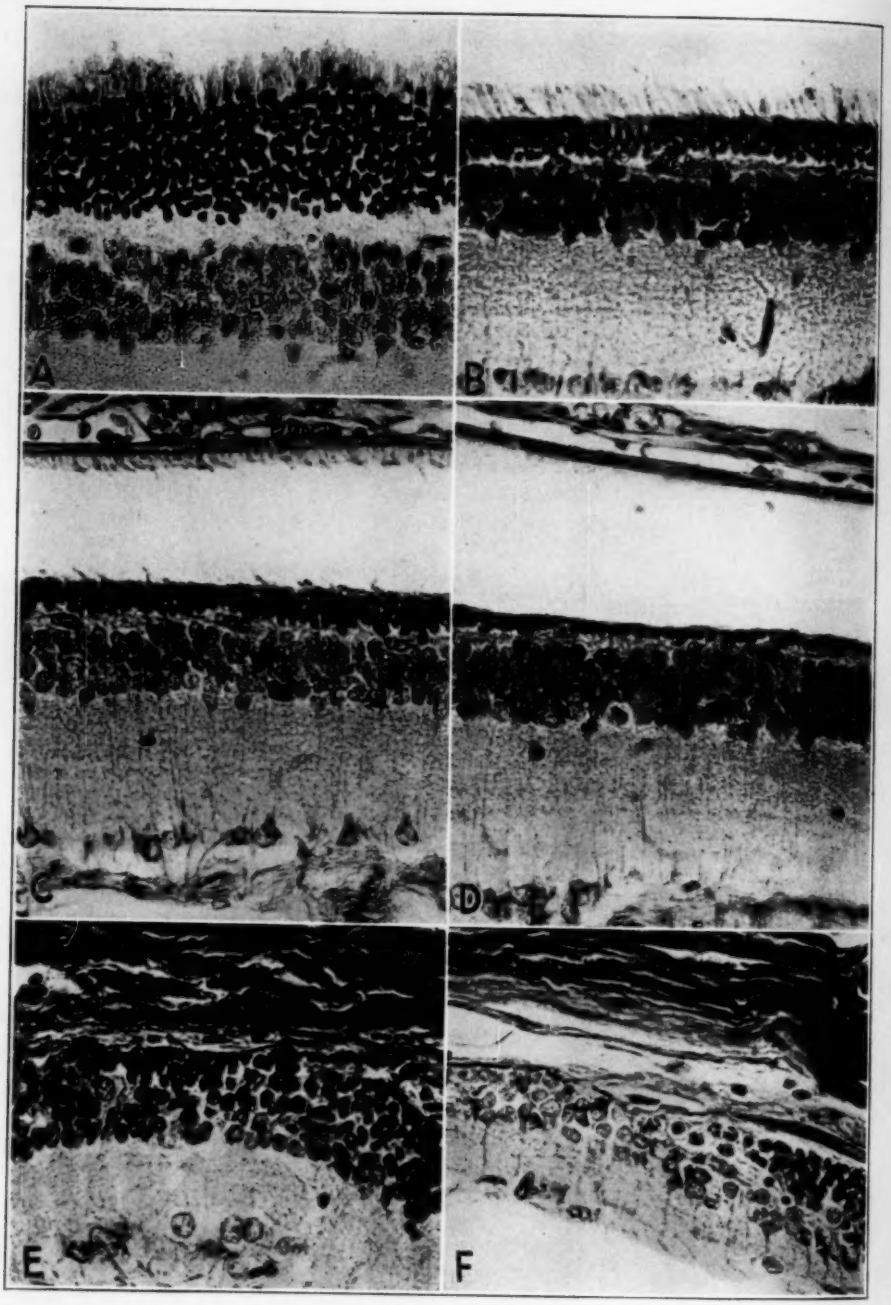

Figure 2

(See legend on opposite page)

spersed among these, were regions showing partial or complete degeneration of all layers sclerad to the inner molecular layer. In the latter places, a few degenerating visual cell nuclei generally remained, the external limiting membrane was completely absent and the internal nuclear layer was reduced to two or three rows of degenerating bipolar cells (fig. 2 *E*). What remained of the retina lay close to the choriocapillaris, separated from it only by the pigmented epithelial cells, which in such regions had a flattened, squamous form not unlike that of fibroblasts. Retinal rosettes, similar to those described previously by me, were found in 9 retinas. Two to four of what appeared to be desquamated pigmented epithelial cells, similar to those previously mentioned, were invariably found among the degenerating visual cells which filled the lumens of these rosettes.

The "recovery" eyes of this subgroup showed, like those of the first subgroup, that peripheral regions which suffered only slight damage become completely normal after ten to twenty-one days of recovery. Regions just peripheral to the fundus, which in the "deficient" eyes had shown more advanced degeneration of the visual cells and beginning degeneration of the outer nuclear layer (fig. 2 *A*), showed a remarkable degree of repair after ten to eighteen weeks of recovery. Figure 1 *F* shows a section from a region of the "recovery" retina corresponding to the "deficient" one illustrated in figure 2 *A*. The animal from which this

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EXPLANATION OF FIGURE 2

A, section of the periphery of the retina of a rat suffering from severe vitamin A deficiency. Nothing remains of the outer segments of the rods except a few degenerating fragments. The inner segments and some of the visual cell nuclei are also degenerating. The external limiting membrane is not present, and the nuclei of the outer nuclear layer are pushed apart, giving this layer an irregular, disorderly appearance. Compare with figure 1 *E*, which shows the corresponding region from the other eye of the animal after eighteen weeks of recovery. *B*, section from the fundus of the "recovery" retina shown in figure 1 *E*. The corresponding region from the "deficient" retina of this animal showed only slightly less degeneration than that illustrated in *C*. Note the regenerated rods appearing here as thin, pale-staining filaments extending from the greatly reduced outer nuclear layer. Note also that the outer molecular layer has almost completely disappeared. *C*, section from the fundus of the retina of a vitamin A–deficient rat. The retina shows characteristic detachment from the epithelial pigment layer. Only a few fragments of the inner segments of the rods remain, the outer nuclear layer is greatly reduced and the outer molecular layer is almost completely absent. *D*, section through the fundus of a twelve week "recovery" retina, from the animal whose "deficient" retina is shown in *C*. The pigmented epithelium has remained intact, and the outer nuclear layer has been further reduced, until only one row of nuclei remains. *E*, section through the fundus of the retina of a vitamin A–deficient rat, showing loss of the entire visual cell layer, most of the inner and outer nuclear layers and all of the outer molecular layer. The pigmented epithelial cells, though not well shown here, remained as a continuous row of flattened, squamous cells. *F*, section from the fundus of a twelve week "recovery" eye, from the animal whose "deficient" retina is shown in *E*. Compare the right and left sides of the section, noting that on the right the epithelial pigment layer and parts of the inner and outer nuclear layers remain, whereas on the left the pigmented epithelial layer, the outer nuclear layer and the outer molecular layer are completely absent and much of the inner nuclear layer has degenerated.

retina was obtained had been fed adequately for eighteen weeks after enucleation of the "deficient" eye. The part of the retina shown here appeared to be entirely normal except that the outer segments of the rods were slightly longer, more slender and less heavily stained than normal ones. Furthermore, the rod population seemed to be considerably sparser than normal. Other retinas showed approximately the same features after ten, twelve or fourteen weeks of recovery. In all such retinas, the outer segments of the rods never seemed to be of normal thickness, though frequently normally stained ones might be seen.

Areas of retinas which had undergone more severe damage did not show much repair even after eighteen weeks of recovery. The "recovery" retinas of animals whose "deficient" retinas had shown degeneration involving several rows of the outer nuclear layer, with only scattered inner segments of rods remaining, showed no increase in the number of nuclei comprising the outer nuclear layer. However, in many instances, a few scattered rods had, apparently, regenerated. These rods were pale staining, thin and shriveled in appearance, but inner and outer segments were readily distinguishable in all of them (fig. *2 B*).

Retinas similar to that shown in figure *2 C*, in which all but two or three rows of the outer nuclear layer had degenerated, showed no repair at all. In fact, most of the "recovery" retinas of the animals showing such "deficient" retinas appeared to have degenerated further during the recovery period (fig. *2 D*). One extremely interesting feature of these retinas was that, although only one row of nuclei remained of the outer nuclear layer, the pigmented epithelium adjoining it always remained intact.

Of the 8 animals with "deficient" retinas similar to that illustrated in figure *2 E*, with degeneration of all the layers external to the inner molecular layer, only 4 survived long enough to permit a study of the "recovery" eye. However, the survivors were maintained on an adequate diet for ten and twelve weeks before the "recovery" eye was excised. Areas in these retinas which had suffered only slight damage showed complete recovery, but interspersed among them were regions similar to those shown in figure *2 F*, showing no recovery. In places, part of the outer nuclear layer remained; the outer molecular layer was absent, so that what was left of the inner nuclear layer was in direct contact with the outer nuclear layer. It will be observed that here the pigment epithelium was still intact, but in the adjacent area, where nothing remained of the outer nuclear layer, the pigmented epithelial layer was absent. There appears to be a very close relationship between the outer nuclear layer and the epithelial pigment layer, for the latter invariably was intact as long as the least sign of an outer nuclear layer remained and was never present in the complete absence of the outer nuclear layer.

COMMENT

Aberle,[20] Mellanby [27] and others have noted that lesions of the spinal cord and peripheral nerves, beginning with degeneration of myelin, did not occur in rats suffering from acute vitamin A deficiency but only in those suffering from long-continued avitaminosis A. And I [16] had reported previously that the first structural change occurring in the retinas of vitamin A–deficient rats was the loss of the dark-staining material of the outer segments of the rods, which was described by

27. Mellanby, E.: Xerophthalmia, Trigeminal Degeneration and Vitamin A Deficiency, J. Path. & Bact. **38**:391-407, 1934.

Arey [28] as greatly resembling the myelin of the nervous system. It is not surprising, therefore, that the retinas of rats suffering from an acute, severe avitaminosis A for only a short time do not show any structural changes other than edema.

Although in 1939 I stated that the clinical manifestations of avitaminosis A did not serve as a reliable guide to the amount of degeneration to be encountered in the retina, I also stated that the early changes noted in the visual cells were characteristic of moderate vitamin A deficiency. In the light of the present experiments that view must be revised. It appears now that even the earliest change occurring in the retinas of vitamin A–deficient rats should be regarded as one of the late manifestations of a severe, long-continued deficiency. It also seems probable that once the visual cells have begun to degenerate, the degeneration progresses fairly rapidly through all the layers of the retina sclerad to the inner molecular layer.

In none of the retinas studied (either in 1939 or at the present time) was degeneration of the inner molecular layer, of the ganglion cells or of the nerve fiber layer observed, although all layers external to these might have been completely destroyed. This observation immediately suggests that interference with the choroidal blood supply, on which the outer retinal layers are metabolically dependent, may have been the direct cause of the degeneration. However, the choroidal vessels always appeared to be patent and entirely normal, even when the connective tissue between them was noticeably increased in amount. It is perhaps more likely that complete degeneration of the retina might have occurred if the animals could have survived on the vitamin A–free diet for a sufficient length of time.

One apparently must fall back on the rather unsatisfactory explanation that vitamin A is necessary for maintaining the health of the visual cells and their associated structures. Even this noncommittal explanation would be questioned by Popper and Greenberg,[29] who reported that the amount of vitamin A normally present in the visual cell layer and the epithelial pigment layer of the retina is shown by fluorescence microscopy to be only slightly reduced in vitamin A–deficient rats when all other organs of the body are entirely free of vitamin A. This finding would also seem to invalidate the theory that night blindness is caused by the absence of vitamin A, which has been

28. Arey, L. B., in Cowdry, E. V.: Special Cytology: The Forms and Functions of the Cell in Health and Disease, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1224.

29. (*a*) Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, Arch. Path. **32**:11-32 (July) 1941. (*b*) Greenberg, R., and Popper, H.: Demonstration of Vitamin A in the Retina by Fluorescence Microscopy, Am. J. Physiol. **134**:114-118, 1941.

generally recognized as a substance essential for the formation of visual purple. However, it should be pointed out that Popper and Greenberg [29a] found that young rats were completely free of vitamin A in all organs of the body except the eyes only fifteen days after they were weaned on the vitamin A–free diet. Although no one would question that these rats were extremely vitamin A deficient or that severe—often fatal—symptoms of avitaminosis A may appear within fifteen to thirty-two days after the feeding experiments are started, the present study has shown that only a chronic, long-continued avitaminosis A produces structural changes in the retina. It seems logical to assume, therefore, that only a corresponding degree of avitaminosis A would deplete completely the vitamin A stores of the eye tissues. Furthermore, Greenberg and Popper [29b] observed the vitamin A fluorescence in the visual cell and epithelial pigment layers of the retina—layers which had completely degenerated in many of the retinas of the present study. Their conclusion that there is a specific distribution of vitamin A in the retina which is practically independent of the nutritional status of the animal seems to be open to question pending further investigation.

A comparison of the eyes removed from vitamin A–deficient rats with those removed from the same animals after various periods of adequate feeding has revealed that the visual cells of the rat are capable of a certain amount of repair.

"Deficient" retinas of certain rats—or parts of "deficient" retinas—were found in which the rods had undergone only early structural changes, characterized by a thinning of the outer segments and loss of the characteristic staining reaction (figs. 1 *B* and *E*). These changes may be attributed to the complete absence, or the extreme sparsity, of the dark-staining "myeloid" material normally contained within the membrane of the outer segments of the rods. "Recovery" retinas from such animals showed an extraordinary degree of repair after only twenty-four hours of recovery (fig. 1 *C*) and practically a complete return to the normal condition after twenty-one to twenty-eight days (fig. 1 *D*). I believe that the extremely rapid recovery occurring in twenty-four hours in these animals should be regarded, not as the regeneration of completely new outer segments, but rather as the repair of damaged ones. For the damage here appeared to be chiefly an absence or sparsity of outer segment material and the repair a replacement of that material. Furthermore, these observations seem to be entirely compatible with the results in clinical and experimental cases of human dietary night blindness in which the administration of vitamin A brought about a rapid return to normal vision (Wald, Jehgers and Arminio,[4] Wald and Steven,[5] Booher, Callison and Hewston,[6] Steven and Wald [7] and Lewis and Haig [8]). For, although the night blindness

in such cases is regarded quite properly as a functional disorder produced by the lack of vitamin A, a substance essential for the formation of visual purple, it is not surprising that the rods, in which formation of visual purple is known to occur, should exhibit some structural evidence of their dysfunction. Likewise, a return to normal function is indicative of the presence of structurally normal visual cells.

Parts of the retina in other animals, which exhibited considerably more damage, with complete degeneration of the outer segments of the rods, partial degeneration of the inner segments of the rods and some destruction of the nuclei of the visual cells (fig. 2 *A*), recovered to a remarkable degree, but only after ten to eighteen weeks of adequate feeding. Some of the rods in these retinas (presumably those whose nuclei degenerated) apparently were lost, but the majority of them appeared almost normal after ten to eighteen weeks (fig. 1 *F*). Although these "repaired" rods still were thinner and less heavily stained than normal, it is entirely possible that they might have become completely normal after a longer period of recovery. I believe that here, in contrast to the retinas described in the preceding pages, the rods had regenerated completely new outer segments, and perhaps in some instances new inner segments as well. Furthermore, these findings offer a reasonable explanation for the behavior in certain cases of night blindness described by Hecht and Mandelbaum [10] and MacDonald and Adler.[11] In these cases, the visual threshold returned to normal only after weeks and months of vitamin A replacement therapy, indicating that the long-continued night blindness was not merely a functional disorder produced by the absence of a substance essential for the formation of visual purple or by a minor, rapidly reparable change in the visual cells. On the other hand, the slow return to normal vision seems more indicative of a recovery process involving the complete regeneration of structures such as the outer and inner segments of the rods.

No regeneration of visual cell nuclei was found in any of the present retinas. However, the retinas in which only three or four rows of visual cell nuclei and fragments of inner segments of rods remained underwent no further degeneration during the recovery period and, in fact, showed an abortive attempt at regeneration of rods from the few remaining visual cell nuclei (fig. 2 *B*). These regenerated rods were abnormal, shrunken structures, but inner and outer segments could be distinguished readily in them.

No repair at all was found in retinas which showed almost complete destruction of the outer nuclear and outer molecular layers (figs. 2 *C* and *D*) or in those which showed degeneration including the inner nuclear layer (fig. 2 *E* and *F*). Although eighteen weeks was the longest recovery period for the animals exhibiting such retinas, it seems

likely that, in due time, these lesions would have become progressively worse rather than better. It is possible that instances such as these may explain the permanency of the night blindness found by Moore, Huffman and Duncan,[12] Hart and Guilbert[13] and Moore[14] in cattle.[30]

It appears then that although early structural changes in the outer segments of rods are repaired with great rapidity on the administration of vitamin A and, although lesions involving complete degeneration of such segments are capable of repair after a recovery period of weeks or months, lesions which involve the greater part of the outer nuclear layer, or more, are irreparable. These findings offer a reasonable explanation for the diversity of results obtained in cases of human and bovine dietary night blindness.

SUMMARY

1. The retinas of rats suffering from acute, severe, avitaminosis A for a short time show no structural changes other than a general edema.

2. The retinas of rats suffering from severe avitaminosis A over a long period show a degeneration which begins in the visual cells and progresses, in order, through the outer nuclear layer, the pigmented epithelial layer, the outer molecular layer and the inner nuclear layer.

3. Outer segments of rods which have undergone only slight degenerative changes as a result of avitaminosis A show a remarkable degree of repair after only twenty-four hours of vitamin A therapy and a practically complete return to the normal condition after twenty-one to twenty-eight days of recovery.

4. The outer segments of rods (and possibly the inner segments as well) which have completely degenerated as a result of vitamin A deficiency are capable of regeneration in rats that are adequately fed for a period of ten to eighteen weeks following the deficiency.

5. Lesions of the rat retina which involve the greater part of the outer nuclear layer, or more, are irreparable after ten to eighteen weeks of recovery from vitamin A deficiency.

The possible relationship between the observations made in the present study and those made in cases of human dietary night blindness is discussed.

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30. Although these writers attributed the blindness of the cattle studied to the optic nerve degeneration they observed, it seems likely that this degeneration occurred secondarily to lesions in the retina.

STUDIES WITH MICROCRYSTALLINE SULFATHIAZOLE

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Recently a new form of the sulfonamide compounds was developed. This is the microcrystalline form produced by either sonic vibration or use of some rapid mixing device.[1] The chief difference from the ordinary sulfonamide compounds is the smaller size of the crystals, which renders more surface available and also permits passage through a 26 gage needle of concentrations as high as 20 per cent.

Studies were undertaken in an attempt to evaluate this new physical property in ophthalmology. In a recent article [2] we showed that the ratio between the concentrations of sulfathiazole (2-[paraaminobenzene-sulfonamido]-thiazole) in the aqueous and in the blood of cats with approximately the same with intraperitoneal injection of microcrystalline and oral administration of macrocrystalline sulfathiazole.

Both Guyton [3] and Chinn and Bellows [4] have demonstrated the relatively greater penetration of sulfanilamide than of its derivatives when applied locally. They showed that sulfathiazole penetrated into the aqueous in very small quantities. To determine whether the smaller size of the crystals, resulting in greater surface area, might increase the penetration of sulfathiazole, a comparative study was done on 16 normal cats' eyes, a 5 per cent emulsion base ointment of macrocrystalline sulfathiazole and of microcrystalline sulfathiazole being used. The 5 per cent macrocrystalline ointment was placed in the right eyes of 8 cats. This was done every half-hour for six doses. The micro-

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From the Department of Ophthalmology, University of Pennsylvania School of Medicine.

The microcrystalline preparations used in this study were supplied by and the work aided by a grant from the Smith, Kline & French Laboratories.

1. Chambers, L. A.; Harris, T. N.; Schumann, F., and Ferguson, L. K.: The Use of Microcrystals of Sulfathiazole in Surgery, J. A. M. A. **119**:324 (May 23) 1942.

2. Scheie, H. G., and Leopold, I. H.: Penetration of Sulfathiazole into the Eye, Arch. Ophth. **27**:997 (May) 1942.

3. Guyton, J. S.: Local Use of Sulfanilamide Compounds in the Eye, Am. J. Ophth. **24**:292, 1941.

4. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, Arch. Ophth. **27**:34 (Jan.) 1942.

crystalline sulfathiazole was similarly applied to the left eyes of the 8 cats. All animals were anesthetized with sodium amytal, 50 mg. per kilogram of body weight. Specimens of aqueous were taken by limbal puncture four hours after the initial application of sulfathiazole, each eye being thoroughly washed with physiologic solution of sodium chloride before the specimen was taken. Determinations of sulfathiazole were done by the method of Bratton and Marshall [5] and are recorded in table 1. Although the concentration in the aqueous was always slightly greater in the eyes receiving the microcrystalline sulfathiazole, the difference was not significant.

Because of the ease of injecting a neutral suspension of microcrystalline sulfathiazole through a fine hypodermic needle, subconjunctival administration of 0.5 cc. of 10 per cent suspension of microcrystalline sulfathiazole was attempted in the normal right eyes of 8 cats anesthetized

TABLE 1.—*Level in Aqueous After Use of Macrocrystalline and Microcrystalline Ointment*

Animal No.	Macrocrystalline Form (Right Eye); Mg. per 100 Cc.	Microcrystalline Form (Left Eye); Mg. per 100 Cc.
1	0.53	0.58
2	0.86	0.92
3	0.50	0.59
4	0.46	0.79
5	0.59	0.66
6	0.66	0.79
7	0.58	0.64
8	0.60	0.68

with sodium amytal. At the same time the left eye received the same dose plus 0.5 cc. of 1:1,000 solution of histamine hydrochloride subconjunctivally, and all eyes were thoroughly washed with physiologic solution of sodium chloride. Specimens of aqueous were taken by limbal puncture four hours after the initial injection. The results are recorded in table 2.

When vasodilatation is produced by histamine, the amount which penetrates into the aqueous is definitely increased. We [2] showed that a similar increase in the penetration into the aqueous from the blood stream occurred in the presence of vasodilatation and that ocular infection increased the penetration even more.

These findings reveal that the subconjunctival injection of microcrystalline sulfathiazole did not increase the penetration of sulfathiazole into the aqueous in normal cats' eyes over that obtained by the use of a 5 per cent ointment (table 1).

5. The chemical determinations were done by Mr. David Stevens at Children's Hospital.

To investigate the penetration of 5 per cent suspension of microcrystalline sulfathiazole, 16 normal cats' eyes were used. Two drops of this suspension was placed in the right eyes of 8 cats every fifteen minutes for three and one-half hours. Two drops of the suspension with 1 drop of a 0.1 per cent solution of duponol ME dry [5a] was placed in the left eyes of the same 8 cats every fifteen minutes for three and one-half hours. At the end of four hours all cats were anesthetized with sodium amytal; all

TABLE 2.—*Level in Aqueous After Subconjunctival Injection of Suspension With and Without Histamine*

Animal No.	Microcrystalline Sulfathiazole (Right Eye); Mg. per 100 Cc.	Microcrystalline Sulfathiazole plus Histamine Hydrochloride (Left Eye); Mg. per 100 Cc.
1	0.95	2.38
2	0.50	1.12
3	0.33	1.12
4	0.46	1.39
5	0.26	1.06
6	0.00	1.06
7	0.20	1.10
8	0.46	1.42

TABLE 3.—*Level in Aqueous After Application of Suspension With and Without Detergent*

Animal No.	5% Suspension of Microcrystalline Sulfathiazole (Right Eye); Mg. per 100 Cc.	5% Suspension of Microcrystalline Sulfathiazole plus 0.1% Duponol ME Dry (Left Eye); Mg. per 100 Cc.
1	0.06	1.59
2	0.33	2.57
3	0.26	2.11
4	0.40	2.05
5	0.20	2.00
6	0.31	2.16
7	0.35	2.40
8	0.40	2.22

the eyes were thoroughly washed with physiologic solution of sodium chloride and specimens of aqueous were taken by limbal puncture. The results are recorded in table 3. No cornea stained with fluorescein at the time the specimen of aqueous was taken. It is evident from the values shown in the table that a 5 per cent suspension of microcrystalline sulfathiazole does not penetrate readily into the aqueous of normal cats' eyes. However, when a detergent, such as duponol ME dry, was used, there was a definite increase in the level of sulfathiazole in the aqueous.

5a. Duponol is a registered trademark designating certain higher aliphatic alcohol sulfates and their derivatives which are used as detergents. Duponol ME dry is derived from technical lauryl alcohol and contains a minimum of electrolytes.

O'Brien and Swan [6] have demonstrated the increased penetration of carbaminoylcholine chloride by use of detergents.

The same experiment was repeated with 5 per cent microcrystalline sulfathiazole ointment with an emulsion base. Four cats were anesthetized with sodium amytal and the ointment alone applied to the 4 right eyes. The ointment plus 1 drop of 0.1 per cent solution of duponol ME dry was applied to the 4 left eyes. Applications were made every half-hour for six doses. After four hours the eyes were thoroughly washed with physiologic solution of sodium chloride and specimens of aqueous were taken. No cornea stained with fluorescein at the time these specimens were taken. The results are recorded in table 4.

Apparently the detergent also increased the penetration of the ointment form. The increase was not as striking as it was for the 5 per cent suspension.

TABLE 4.—*Level in Aqueous After Use of Ointment With and Without Detergent*

Animal No.	5% Microcrystalline Sulfathiazole Ointment (Right Eye); Mg. per 100 Cc.	5% Microcrystalline Sulfathiazole Ointment plus 0.1% Duponol ME Dry (Left Eye); Mg. per 100 Cc.
1	0.50	0.86
2	0.58	0.93
3	0.66	1.25
4	0.60	1.06

Because a suspension of microcrystals readily passes through a 26 gage needle, injections into the vitreous were attempted as a means of rapidly obtaining high intraocular concentrations of sulfonamide compounds.

A 5 per cent suspension of microcrystalline sulfanilamide, 0.5 cc., was injected into the vitreous of each eye of 2 cats anesthetized with sodium amytal. Samples of aqueous were drawn from one eye of each cat after four hours and from the other eye after sixteen hours. The same procedure was repeated for sulfathiazole and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine).

In all eyes, immediately after injection the cornea became hazy owing to the rise in intraocular tension. This effect disappeared in six hours.

The eyes treated with sulfanilamide and sulfathiazole showed a haze of the vitreous, which largely subsided in thirty-six hours and remained as opacities in the vitreous for four days. At the end of the first week no

6. O'Brien, C. S., and Swan, K. C.: Carbaminoylcholine Chloride in Treatment of Glaucoma Simplex, Arch. Ophth. **27**:253 (Feb.) 1942.

sign of opacities in the vitreous or retinal damage could be seen with an ophthalmoscope. After fourteen days the eyes were enucleated and submitted to pathologic study.[7] Each eye showed a clear vitreous but also a small area of focal retinal degeneration. These areas were smaller in the sulfathiazole-treated eyes. The perforation in the sclera marking the site of entry of the injecting needle was in each instance either caught within the area of retinal damage or situated immediately adjacent.

Two of the sulfapyridine-treated eyes reacted clinically exactly like the sulfanilamide-treated and the sulfathiazole-treated eyes, but 2 eyes had definite signs of iridocyclitis, which had largely cleared after fourteen days, and on pathologic study all of these eyes showed changes in the vitreous and large areas of retinal degeneration.

The p_H of all suspensions was approximately 6 +.

Apparently a 5 per cent suspension of microcrystalline sulfathiazole or sulfanilamide can be injected into the vitreous of the cat with little

TABLE 5.—*Level in the Aqueous and in the Blood After Injection of Sulfanilamide, Sulfathiazole and Sulfapyridine into Vitreous*

		Aqueous; Mg. per 100 Cc.		
Drug	Animal No.	Right Eye, 4 Hours After Injection	Left Eye, 16 Hours After Injection	Blood; Mg. per 100 Cc. 16 Hours After Injection
Sulfanilamide.....	1	12.0	1.8	1.19
	2	14.1	2.6	1.39
Sulfathiazole.....	3	10.3	5.2	0.46
	4	9.1	5.1	0.50
Sulfapyridine.....	5	11.1	0.4	0.4
	6	Aqueous clotted	0.4	0.36

change in the vitreous but with a small but definite area of retinal degeneration. Five per cent suspension of microcrystalline sulfapyridine causes much more pathologic change.

Table 5 shows the concentration in the aqueous at four hours and at sixteen hours after the initial injection. These results indicate that a high intraocular concentration of a sulfonamide compound can be obtained by injection into the vitreous. The concentration is still high after four hours but falls rapidly and is not maintained after sixteen hours. Sulfathiazole disappears through the aqueous-blood barrier at a slower rate than sulfanilamide or sulfapyridine. The irritation in the sulfapyridine-treated eyes may account for the more rapid disappearance from the intraocular fluids of sulfapyridine than of sulfanilamide.

7. The pathologic studies were done at Children's Hospital by Dr. Irving J. Wolman.

Bellows and Chinn,[8] Leibman and Newman[9] and Scheie and Souders[10] have shown that orally administered sulfanilamide can produce a high intraocular concentration within four hours. It has also been shown that a high intraocular level of sulfathiazole can be obtained in the presence of intraocular infection within four hours.[2] Therefore the only advantages to be gained by intravitreous injection of sulfathiazole and of sulfanilamide would be the immediate high intraocular concentration of the drug. Weighed against this advantage is the disadvantage of producing retinal degeneration. Whenever an intravitreous injection is indicated, sulfathiazole would probably be the drug of choice, as it produces the least destruction.

Because of the ease of injecting a 5 per cent suspension into the lacrimal sac, 5 patients with purulent dacryocystitis were treated with a 5 per cent microcrystalline suspension. Sulfapyridine was chosen for 3 and sulfathiazole for 2 because cultures in all cases showed pneumococci. Injections of 2 cc. were made daily, and in all cases after three daily injections the discharge had cleared and cultures were negative, although the nasolacrimal ducts still were obstructed.

In a sixth case of purulent dacryocystitis, culture showed both pneumococci and Haemophilus influenzae. After two injections of 5 per cent microcrystalline sulfapyridine, the pneumococci disappeared, but the influenza bacillus persisted in spite of additional injections of sulfathiazole and sulfadiazine.

Hemolytic streptococcus infection in 1 case failed to respond to five daily injections of 5 per cent sulfapyridine but did clear after two injections of 5 per cent sulfanilamide.

These findings may indicate a satisfactory method of temporarily controlling purulent dacryocystitis, provided one knows the offending organism and chooses the appropriate sulfonamide compound for therapy.

SUMMARY

The microcrystalline form of sulfonamide compounds has been investigated with the following results:

1. Microcrystalline sulfathiazole ointment penetrated into the aqueous of normal cats' eyes slightly but not significantly more readily than macrocrystalline sulfathiazole ointment.

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8. Bellows, J. G., and Chinn, H.: Penetration of Sulfathiazole in the Eye, Arch. Ophth. **25**:294 (Feb.) 1941.

9. Leibman, S. D., and Newman, E. H.: Distribution of Sulfanilamide and Its Derivatives Between Blood and Aqueous, Arch. Ophth. **26**:472 (Sept.) 1941.

10. Scheie, H. G., and Souders, B. F.: Penetration of Sulfanilamide and Its Derivatives into Aqueous Humor of the Eye, Arch. Ophth. **25**:1025 (June) 1941.

2. Microcrystalline sulfathiazole suspension did not penetrate into normal eyes any more readily than the ointment form.

3. Subconjunctival injection of microcrystalline sulfathiazole suspension did not increase the concentration reaching the aqueous.

4. Chemical vasodilatation increased the concentration in the aqueous of subconjunctivally administered microcrystalline sulfathiazole.

5. A detergent increased the penetration into the aqueous of both the suspension and the ointment form, affecting the suspension more than the ointment.

6. Microcrystalline sulfathiazole, sulfanilamide and sulfapyridine when injected into cats' vitreous as a means of obtaining high intraocular concentrations produced retinal damage.

7. Microcrystalline sulfathiazole was the least and microcrystalline sulfapyridine the most destructive.

8. The microcrystalline form may be a definite aid in clearing purulent dacryocystitis.

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OPTOCHIASMIC ARACHNOIDITIS

REPORT OF THREE CASES

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Although chronic arachnoiditis involving the spinal cord was described by Spiller, Musser and Martin [1] in 1903 and by Horsley [2] in 1909, the possibility that arachnoiditis might affect the optic nerves and chiasm has only recently attracted the attention of ophthalmologists. Despite excellent descriptions of optochiasmic arachnoiditis by Heurer and Vail,[3] Craig and Lillie,[4] Vail [5] and Lillie,[6] there are still too few ophthalmologists who recognize the importance of the disease, its dire consequences to vision if not diagnosed or suspected and the excellent results that may be obtained by surgical intervention.

Doubtless some of the apathy may be attributed to a misconception of the symptoms and signs of the disease. Visual loss and headache are in the great majority of cases the only symptoms complained of. The visual loss may be in one eye or in both. It may be more advanced in one eye than it is in the other; it may be gradual over a period of months or abrupt. The headache has no characteristic. Frequently it is bifrontal, occurring in the late afternoon and aggravated by close work, so that it may easily be mistaken for the headache caused by a refractive error.

The fundi may be completely normal, or examination may disclose a choked disk or an optic nerve atrophy of either the primary or the secondary type. Vail stated that the appearance of atrophy of the disk

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Read before the Chicago Ophthalmological Society April 20, 1942.

From the Department of Ophthalmology, Milwaukee County Hospital.

1. Spiller, W. G.; Musser, J. H., and Martin, E.: A Case of Intradural Spinal Cyst, with Operation and Recovery, Univ. Pennsylvania M. Bull. **16**:27-31 (March) 1903.

2. Horsley, V.: Chronic Spinal Meningitis, Brit. M. J. **1**:513-517 (Feb. 27) 1909.

3. Heurer, G. J., and Vail, D. T., Jr.: Chronic Cisternal Arachnoiditis Producing Symptoms of Involvement of the Optic Nerves and Chiasm, Arch. Ophth. **5**:334-349 (March) 1931.

4. Craig, W. M., and Lillie, W. I.: Chiasmal Syndrome Produced by Chronic Local Arachnoiditis, Arch. Ophth. **5**:558-574 (April) 1931.

5. Vail, D.: Optochiasmic Arachnoiditis, Arch. Ophth. **20**:384-394 (Sept.) 1938.

6. Lillie, W. I.: Prechiasmal Syndrome Produced by Chronic Local Arachnoiditis, Arch. Ophth. **24**:940-947 (Nov.) 1940.

which lies between the primary and the secondary type of atrophy is highly suggestive of arachnoiditis involving the chiasm. In this type the outline of the disk is sharply defined and the lamina cribrosa is visible, but the caliber of the vessels is markedly reduced. In 1 case in this series the fundus picture was such as Vail described. If there are pathologic changes in the two fundi, they are almost always identical; if the change occurs in one eye only, the other is usually normal.

Any type of field defect may be encountered. Bollack, David and Peuch [7] stated that central scotoma occurs in 31 per cent of cases, concentric contraction in 23 per cent and temporal loss in only 17 per cent. Any combination of these field defects may be discovered, or the field in one eye may be entirely normal. Some observers state that a characteristic finding, if indeed this disease has anything characteristic, is that the field changes fluctuate and change from time to time. This, however, is also true of the syndrome accompanying tumor in the chiasmal region and is without significance.

The importance of encephalography as a diagnostic aid has been emphasized by Lillie. He reported 3 cases in which the correct preoperative diagnosis was made with the help of encephalography. When one desires to visualize the subarachnoid space, encephalography, of course, is the method of choice. However, this type of examination is fraught with difficulties. It is a technically arduous procedure and requires the closest cooperation between the neurologist or neurosurgeon and the roentgenologist if technically perfect films are to be secured, for the slightest rotation of the head from the midline will result in errors of interpretation. Positive results of encephalography, as Lillie maintained, are invaluable, but negative results do not preclude the possibility of arachnoiditis. At any rate, the procedure should be used more frequently in the future than it has been used in the past.

Recently Hausman [8] has called attention to the important role that syphilis plays in arachnoiditis. He divided the syphilitic forms of the disease into three distinct groups. In the first group are found bilateral primary optic nerve atrophy, heteronymous field defects, heteronymous visual defects or almost total blindness and a normal ventricular system without evidence of internal hydrocephalus; in the second group, secondary optic nerve atrophy and internal hydrocephalus, and in the

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7. Bollack, J.; David, M., and Peuch, P.: Opticochiasmic Arachnoiditis, translated by P. Fridenberg, Arch. Ophth. **20**:127-130 (July) 1938.

8. Hausman, L.: Syphilitic Atrophy of the Optic Nerve and Papilledema Due to Optochiasmal Arachnoiditis: Indications for Surgical Intervention, Arch. Ophth. **23**:1107-1115 (May) 1940; Syphilitic Arachnoiditis of the Optic Chiasm, Arch. Neurol. & Psychiat. **37**:929-958 (April) 1937; The Surgical Treatment of Syphilitic Optic Nerve Atrophy Due to Chiasmal Arachnoiditis, Am. J. Ophth. **24**:119-132 (Feb.) 1941.

third, papilledema without hydrocephalus. When there is a history of syphilis or serologic evidence of the disease, with a rapid loss of vision frequently terminating in blindness, he said, arachnoiditis should be strongly suspected. He reported good results from surgical intervention in groups 1 and 3 and cited 1 case of a group 1 form in which the patient had been blind for two years and in which vision returned to normal after the adhesions were liberated, although there was no change in the color of the nerve head.

It has been generally known that syphilis is an etiologic factor in this disease, but too little importance has been attached to it, as is best exemplified by the few reported cases. Heretofore when specific fundus disease and field defects were encountered in syphilis, they were almost universally considered to be due to parenchymatous disease of the nerve, regardless of whether or not the patient displayed any neurologic evidence of tabes; the possibility of adhesions about the nerves and chiasm causing the pathologic change was infrequently thought of, and the incident was dismissed by referring the patient to a syphilologist for intensive treatment.

Patients with this type of arachnoiditis should be treated energetically prior and subsequent to surgical intervention, and it obviously is not intended to ridicule treatment of the syphilis but rather to encourage more careful study of the forms of syphilitic optic nerve atrophy, especially when they coincide with Hausman's classification.

REPORT OF CASES

Case 1.—J. S., a boy aged 7, was seen on July 12, 1940, the only complaint being impaired vision for the past two years. The onset of the visual loss was gradual. In the beginning he had difficulty in seeing minute details, and this gradually progressed until he could see only large objects. The child had no difficulty in playing or in getting about in familiar places, but his mother believed that this was because he had been accustomed to playing the games and knew the places. There never had been any complaint of headache or ocular pain. He had no history of dizziness, nausea or vomiting.

He had had measles and pertussis three years before and mumps one year before. These diseases were uncomplicated and ran a regular course, and there was complete recovery. Three years before he was struck on top of the head by a part of a cement mixer. The scalp was lacerated, but he was not unconscious at any time. He was the oldest of four children, his three sisters being 6 years, 5 years and 11 months old respectively. All were well and had had no ocular trouble.

Vision in each eye was limited to perception of hand movement. There was a broad ocular nystagmus. The external examination gave entirely negative results. The pupils were moderately dilated, were equal and round and reacted actively to light directly and consensually. The media were clear. Both nerve heads were chalky white, and the lamina cribrosa was plainly seen. The retinal arteries were decidedly narrowed and were difficult to follow much beyond the disk

margins. The retinal veins were also smaller than normal, but could be followed without difficulty. There were a few patches of fine pigmentation scattered about the central part of each fundus. These pigment spots closely resembled the pigmentation of retinitis pigmentosa.

Owing to eccentric fixation it was impossible to do a field examination. However, when an object was held directly in front of the child he would turn his eyes either to the right or to the left in order to distinguish the object; because of this fact it was postulated that he had a large central scotoma.

General physical examination gave entirely negative results. The Wassermann and the Kline reaction were negative. Complete neurologic study disclosed nothing of importance, and the spinal tap yielded normal fluid. Roentgenologic studies of the optic foramens disclosed destruction of bone in the posterior wall of the orbital canal on the right side. The sella was normal.

A transfrontal craniotomy was done on October 12 by Dr. David A. Cleveland. The ventricle was cannulated at the usual depth, but only a small amount of fluid was obtained. However, considerable subarachnoid fluid was removed. The frontal lobe was elevated and the right optic nerve exposed. There was a veil of tissue like a glassine bag surrounding the chiasm, which when opened allowed the escape of a large amount of subarachnoid fluid. Lying laterally to the optic nerve was an enormous ophthalmic artery, from which an aberrant artery crossed on top of the right optic nerve. The optic chiasm was then entirely exposed, and lying laterally to the left optic nerve could be seen a veil of tissue, which was easily broken. After this was broken through there was an escape of rather a large amount of subarachnoid fluid.

The patient had an uneventful recovery and was dismissed from the hospital on November 7. Examination on Aug. 26, 1941 disclosed no change in his visual acuity. The nystagmus had entirely disappeared, but there were a left convergent strabismus of 35 degrees and a bilateral sixth nerve paralysis. There was no change in the fundus picture.

The features of this case are the bilateral central scotoma and the bilateral optic nerve atrophy, such as Vail described as being suggestive of arachnoiditis.

Leber's disease, arachnoiditis and glioma of the chiasm were the diagnostic possibilities considered, the last because of the destruction of bone in the right optic foramen. The possibility of a craniopharyngioma was ruled out, as no calcification was found on roentgen ray examination. Leber's disease could be eliminated with a fair amount of confidence because the disease occurs infrequently and the family history was entirely negative with respect to it. A differentiation between arachnoiditis and glioma could not be made preoperatively, although the latter seemed the more probable. The correct diagnosis was made at operation.

CASE 2.—D. D., a boy aged 9, was seen on Sept. 26, 1940, the only complaint being poor vision in the right eye which had existed for three months and had been particularly poor the last month.

He had had measles at the age of 5 years and mumps at the age of 4. Both attacks were mild, there were no complications and he made a complete recovery. He had had a yearly attack of bronchitis since he was 3 years old. The attacks

lasted about three or four days, were never severe and always had been uncomplicated. There was no history of injury to the head. He had had his tonsils and adenoids removed one month before.

The vision was 0.1 in the right eye and 1 + 3 in the left. The external examination gave entirely negative results. The pupils were equal and round and reacted actively. The media were clear. The right eye had papilledema of

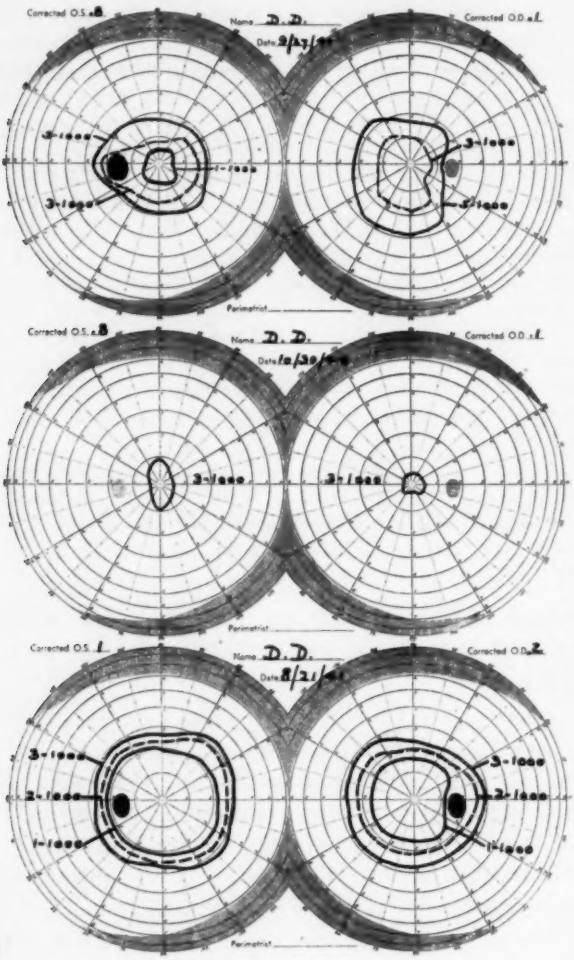

Fig. 1 (case 2).—The fields on admission, just prior to surgical intervention and after intervention.

about 2 D., and the edema extended a short distance into the surrounding retina. There were no hemorrhages or exudates and no vitreous floaters. The left eye was normal. Field examination disclosed an extensive depression in the right eye, more advanced in the temporal half. The 1 mm. object was not seen with this eye. There was also a marked depression of the field in the left eye. The correction

with atropine cycloplegia was as follows: right eye, + 4.00 D. sph. ⌒ + 1.00 D. cyl., axis 120, vision 0.1; left eye, + 0.50 D. sph. ⌒ + 0.50 D. cyl., axis 70, vision 1.

Roentgen ray examination disclosed a normal sella and normal optic foramens. The sinuses showed no pathologic change. Neurologic examination, including a spinal tap, gave entirely negative results.

On October 13 the vision in the right eye was 0.1 and in the left eye 0.6+. The papilledema was greatly increased, and the edema extended far into the surrounding retina. Field examination at this time disclosed an extensive bilateral depression.

A transfrontal craniotomy was done on November 9 by Dr. David A. Cleveland. Surrounding the optic nerves and bridging the chiasm was a heavy membrane. This was freed and removed with no difficulty. At the time of operation, Dr. Cleveland remarked that this was the most definite arachnoiditis that he had ever seen. The child made an uneventful recovery and was dismissed from the hospital on November 18.

On November 23 there was 3 D. of papilledema and definite evidence of secondary optic nerve atrophy. There was no improvement in the vision. On April 17, 1941 the vision in the right eye was 0.4 + 3 and that in the left eye 0.8. There was at this time an advanced secondary atrophy with a dense inverted Y-shaped membrane over the disk. Definite expansion of the fields in both eyes was found on perimetric examination (chart 1). The refraction with atropine on April 24 was as follows: right eye, + 4.00 D. sph. ⌒ + 0.75 D. cyl., axis 135, vision 0.4; left eye, + 0.75 D. sph. ⌒ + 0.50 D. cyl., axis 80, vision 0.8.

Comparatively rapid visual loss with papilledema in one eye and normal vision and a normal fundus in the other eye characterizes this case. The preoperative diagnosis was arachnoiditis, which was confirmed at operation.

Of special interest is the high degree of compound hyperopic astigmatism in the right eye. Some observers believe that high hyperopia with a choked disk is possibly due to edema extending into the macula and beyond, even though the edema cannot be visualized. In this case, however, there was only slight change in the strength of the cylinder after the papilledema had subsided and the secondary optic nerve atrophy was established.

CASE 3.—C. C., a man aged 34, married, was first seen on Oct. 17, 1940 complaining of poor vision and headache. He stated that his vision had always been poor in his right eye but that it had become worse during recent months. There was no history of injury to the head, and otherwise his past history was entirely unimportant.

The vision was 0.1 in the right eye and 0.5 in the left. The ocular examination gave entirely negative results except to disclose a decided fulness of the nasal half of the right disk and a slight engorgement of the retinal veins in the right eye. The left disk and retinal vessels were normal. Field examination disclosed a temporal hemianopsia on the right and a defect in the upper temporal quadrant on the left.

Refraction with homatropine cycloplegia gave the following results: right eye, + 0.25 D. sph. ⌒ — 2.25 D. cyl., axis 30, vision 0.3; left eye, + 0.50 D. cyl., axis 75, vision 0.8.

Physical examination gave entirely negative results except to disclose a slight trace of albumin in the urine. The erythrocyte count was 4,150,000 and the white blood count 13,050. The differential count showed 71 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes and 5 per cent monocytes. Neurologic examination gave entirely negative results. The spinal fluid was under no pressure and

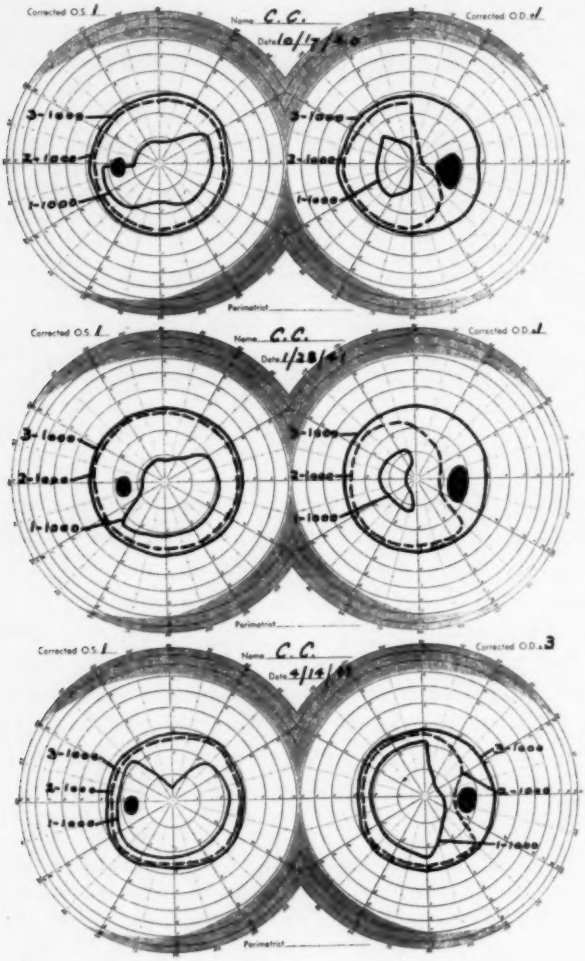

Fig. 2 (case 3).—The fields on admission, prior to surgical intervention and one month subsequent to intervention.

contained no cells. The colloidal gold and the Kline reaction were negative. Roentgen ray examination disclosed a normal sella.

The field changes continued to progress, and the patient was referred for treatment on Feb. 24, 1941. Roentgenograms at this time disclosed a normal sella, but roentgenograms of the optic foramens were suggestive of pathologic change.

The left optic foramen measured 4.5 by 4.5 mm. and its margins were clear, but the right optic foramen measured 5 by 6 mm. and its margins appeared decalcified.

A transfrontal craniotomy was done on March 16 by Dr. Paul C. Bucy. There was no tumor. The arachnoid membrane in the region of the chiasm and the right optic nerve was milky. It was attached to the dura mater over the tuberculum sellae and along the sphenoid ridge by many fine adhesions. There were numerous similar fine cobweb-like adhesions to the chiasm. The arachnoid membrane was carefully dissected away from all these structures. The internal carotid artery was clearly visualized and appeared normal. The right optic nerve was long and appeared smaller in diameter than normal. It had an unusual pale translucent gelatinous appearance.

The patient made an uneventful recovery. The visual fields taken April 14, less than a month after surgical intervention, showed an enormous expansion on both sides (fig. 2).

Normal fundi and bilateral temporal field defects characterize this case.

Arachnoiditis and glioma of the optic chiasm were thought of, and the former was considered most likely because the patient was considerably older than the usual patient with a glioma and there was no evidence of involvement of the hypothalamus.

This case could easily have been dismissed as an instance of a refractive error and amblyopia, and if a field examination had not been done the true nature of the pathologic process would not have been suspected.

SUMMARY

Three cases of optochiasmic arachnoiditis are reported, in all of which the fundus picture and the field defects were dissimilar.

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PIGMENTATION OF OPTIC DISK

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Congenital pigmentation of the optic disk is uncommon in the white race, whereas, according to Oguchi,[1] it is frequently found in the Japanese.

Duke-Elder [2] stated that the pigment on the disk may migrate from the choroid and show itself as a fleck form pigmentation, or the entire disk may be diffusely and uniformly pigmented—black or slate colored.

The pigment may be retinal in origin, occurring because some of the retinal pigment was ensnared in the embryonal glial tissue. More probably, however, the primitive cells of the optic stalk develop the characteristics of pigment-producing epithelium, in a place where pigment cells are not found.

In some cases the optic disk may contain holes or pits within its boundaries. These are localized colobomas and are the result of an outpouching of the secondary optic vesicle through the defective ocular tunics. These are usually on the lower temporal aspect of the disk, rarely on the nasal side and more rarely in the center. The colobomas may be shallow or so deep that the bottoms are out of sight. In some cases they are lined with a layer of pigment derived from the outer layer of the optic cup, but often the appearance of pigment is simulated by the shadows from the depths of the holes. A vessel crossing one of these pits usually dives into its depths, to emerge over the outer edge. Occasionally a cilioretinal artery may emerge from a pit or an opticociliary vein go into one. Vision may or may not be affected.

Mann [3] stated that congenital pigmentation of the disk is rare and that it may be of ectodermal or mesodermal origin. According to her, the areas of pigmentation may appear as dense, isolated placques occupying a sector of the disk and sometimes extending over its margin onto the retina. If the pigment is in the center and surrounds an

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Read before the Brooklyn Ophthalmological Society, May 21, 1942.

1. Oguchi, T.: Melanosarcoma of the Optic Nerve, Arch. f. Ophth. **130**: 427, 1933.

2. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1933, vol. 1, p. 107; 1938, vol. 2, pp. 1265 and 1397.

3. Mann, I.: Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937, pp. 88 and 133.

artery, in her opinion it is probably of mesodermal origin. The pigment may appear as linear markings concentric with the disk margins. The temporal side of the disk is most frequently affected.

Reese [4] pointed out the fact that the fibers of the lamina cribrosa are contiuous with choroidal tissues and that in certain peoples (the Japanese) it is not uncommon to find chromatophores in the disk. He stated the belief that in all cases pigment on the optic disk can be explained as a migration of pigment from the nearby pigment epithelium. He reported a case of pigmentation of the optic nerve following an operation for detached retina.

Sobanski [5] reported one of the rarest of findings, complete pigmentation of the disk. He was able to collect only 2 cases of similar pigmentation, one reported by Hirshberg and the other by Foster. All three authors called the condition a congenital anomaly—a melanosis of the optic nerve.

In a conversation with me, Dr. J. A. de Veer, pathologist at the Brooklyn Eye and Ear Hospital, stated that pigment of the sclera and optic nerve behind the lamina cribrosa is found rather frequently. This would make it difficult to explain the infrequency with which it is found on the disk.

The presence of pigment on the disk may be of more than academic importance, because, though rare, primary melanosarcoma of the optic disk does occur. It is thought that malignant pigmented tumors do not arise from existing pigmented areas or congenital nevi [6] but come from pigment which has migrated into the area involved—acquired pigmentation. However, such a belief is not adhered to by all investigators.

In 1933 Oguchi [1] reported a primary melanosarcoma of the disk. He found only 2 other cases reported in the literature. The patient was a 21 year old man with an oval-shaped pigmented mass on the temporal side of the papilla. It was elevated about 4 D. and spotty in appearance. On section it was found to be a malignant melanosarcoma limited to the disk and optic nerve. Oguchi stated the belief that the tumor was an activation of pigmented tissue on the disk.

Levine [7] reported a primary melanosarcoma of the disk in a 53 year old man. He stated that the tumor originated on the temporal side of the disk, in front of the lamina cribrosa, and grew back to involve

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4. Reese, A. B.: Pigmentation of the Optic Nerve, Arch. Ophth. **9**:560 (April) 1933.

5. Sobanski, J.: Slate-Gray Optic Papilla, Klin. Monatsbl. f. Augenh. **102**: 704 (May) 1939.

6. Reese, A. B.: Precancerous Melanosis and Diffuse Malignant Melanoma of the Cornea, Arch. Ophth. **19**:354 (March) 1938.

7. Levine, J.: Primary Melanosarcoma of the Disc, Arch. Ophth. **14**:229 (Aug.) 1935.

the optic nerve. Pigment-bearing cells were found in the lumen of the central artery. The choroid was not involved. The author declared that the weight of opinion favored the view that such malignant tumors spring from benign melanoma on the disk, whether of epiblastic or of mesoblastic origin.

REPORT OF CASES

CASE 1.—E. M., a woman aged 22, came to the office on May 2, 1941 to change her glasses. She had worn glasses for many years. The vision was 20/100 in the right eye and 20/70 in the left, improved in each eye with a moderate myopic correction to 20/20. The fundi were entirely normal except for the right disk. On the temporal side of the right disk there was a slate gray mass of pigment involving the upper quadrant. A ridge of darker pigment ran through the middle, and the temporal border of the disk was deeply pigmented everywhere except in the middle, where there was a complete absence of pigment. From the border at this point a cilioretinal artery appeared. Going toward the nasal side of the mass were many fine capillaries, which came from the superior temporal vessels. The temporal border of the disk was bounded by a white crescent, and the choroid surrounding the disk was darkly pigmented. The rest of the fundus showed no unusual pigmentation.

A close examination of the pigmented mass showed definitely that it was due not to a hole, or coloboma, of the disk but to a deposit of pigment on the disk. Field examination gave negative results.

CASE 2.—A boy aged 14 came to the office on May 14, 1941 because of frequent headaches. Vision was 20/20 in each eye, and no ocular cause for the headaches was found. Except for the left disk, the fundi were normal. A large part of the outer half of the temporal side of the disk was occupied by a slate-colored pigmented mass, of which the widest diameter was in the middle. The mass was lighter in spots. Into its nasal side entered many fine blood vessels. From the middle of the temporal border a cilioretinal vessel appeared. The temporal border of the disk, unlike that in the first case, was little pigmented, whereas the rest of the border was darkly pigmented.

A white crescent surrounded the temporal border of the disk, and the outer border of the crescent was darkly pigmented. Outside of a small patch of pigment temporal to the disk, the fundus showed no unusual pigmentation. Examination failed to show any holes, or colobomas, in the pigmented area. There was no loss of fields.

CASE 3.—A woman aged 27 came to the office on Nov. 9, 1941 because her eyes felt tired toward the latter part of the day. The vision was 20/25 in the right eye and 20/50 + in the left. The left eye showed a moderate degree of myopic astigmatism, and the vision was corrected to 20/20. Except for the right disk, the fundi were normal. On the temporal side of the disk, beginning slightly above the middle and extending down, was a slate gray mass of pigment. The largest part of the mass was below the middle, and in its widest part it occupied about one-half the width of the temporal half of the disk. The nasal border of the mass was sharply delineated by a narrow white zone. The temporal half of the mass was lighter in color. The temporal border of the disk was fairly pigmented. From the upper part of the pigmented area near the nasal border, a cilioretinal artery appeared. The temporal border of the disk was surrounded by a semiluner area of white in which appeared dark pigment gran-

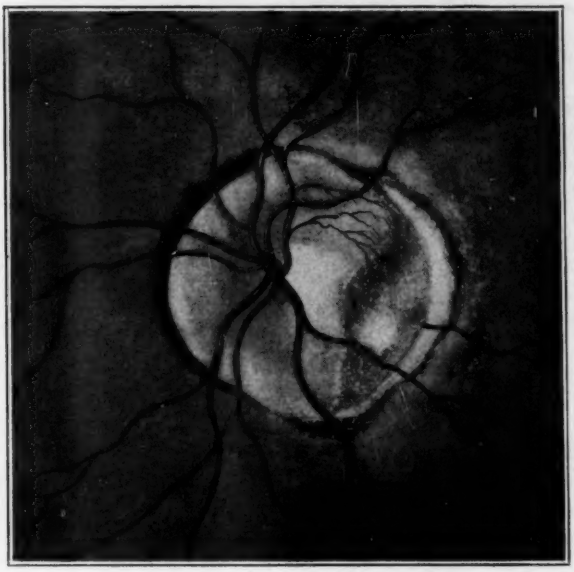

Fig. 1.—The optic disk in case 2.

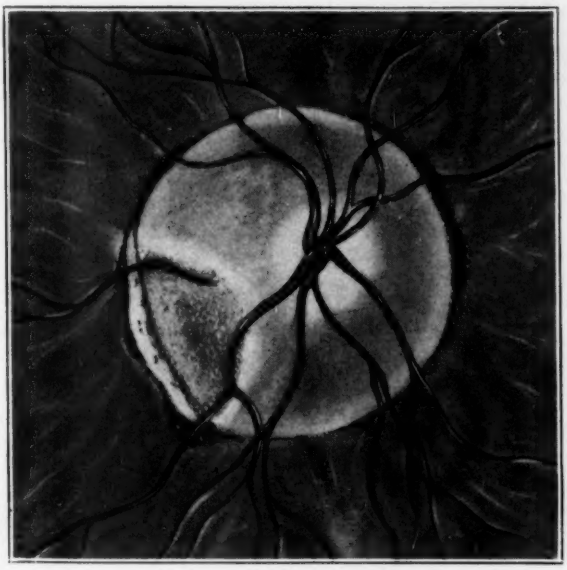

Fig. 2.—The optic disk in case 3.

ules. The outer border of this area was darkly pigmented except at the upper and the lower pole.

Careful search failed to reveal any evidence of holes, or colobomas, in the pigmented area. The fields showed no defect.

The appearance of these pigmented spots gives one the impression that they are congenital pigmented nevi similar to those found elsewhere on the skin. The presence of a cilioretinal vessel in all 3 cases is interesting and of problematic significance. If the pigment on the optic disk is the result of a migration from the surrounding tissue, as Reese declared, then one would expect it to be rather spotty instead of being grouped into one well defined mass, the grouping which is usually reported and is borne out in the cases here presented.

It would seem, therefore, that the explanation given by Duke-Elder and Mann, that the pigment is the result of primitive cells of the optic stalk which have regressed and developed characteristics of pigment-forming cells in a place where they should have developed other functions, is correct. Probably the anatomy of the optic disk, with the sparsity of fibers and vessels on the temporal side, makes this the usual site of predilection.

I hope to have the opportunity of following these cases through many years.

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Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

OPHTHALMIC REQUIREMENTS OF THE MILITARY SERVICES

REVISION FEB. 1, 1943

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NEW ORLEANS

Numerous changes in the visual requirements of the military services and many requests for reprints of the original article have necessitated this revision of "Ophthalmic Requirements of the Military Services" (ARCH. OPHTH. **27**: 1202-1214 [June] 1942). The review is presented also at the request of the American Committee on Optics and Visual Physiology and with the approval and cooperation of the surgeon generals of the Army, Navy and United States Public Health Service.

The purposes of the revision, as of the original article, are (1) to help ophthalmic military and civilian examiners quickly find needed information and (2) to promote greater efficiency in the enforcement of current military regulations concerning ophthalmic requirements. The following order of material is used for each of the military services: (1) functional requirements, (2) qualifying and disqualifying conditions and diseases and (3) references for changes in ophthalmic requirements which have been issued since June 1942 (prior references were presented in the original article).

To understand better the specific changes (1) in visual requirements and (2) in disqualifying conditions and diseases which have occurred since the original article was published, the reader should note that:

1. Voluntary enlistments are steadily being reduced. Selective Service is increasingly the only entering gate for military personnel, forming a huge reservoir of man power to be used as needed.

2. The former requirements of classes 1 A and 1 B of Selective Service are replaced by those of (*a*) general service, enlisted and commissioned personnel, Army and Navy, and (*b*) limited service, enlisted and commissioned personnel, Army and Navy.

3. Women are now accepted as volunteers for limited service in some branches of the Army, Navy and Coast Guard both in the enlisted

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and in the commissioned personnel. They have practically the same visual requirements as men.

4. Recent changes have been made in the scope and operation of the Selective Service System. The registrant is first called and examined by his local Selective Service board. This examination eliminates only those who are obviously unfit for any type of military service and, generally speaking, ends the responsibility of the local board. The inductee is then delivered to the Army and sent to a reception center, where he is examined for final classification, from a physical, mental, educational and occupational standpoint. Next he is assigned to duty with the Army, Navy, Marine Corps or Coast Guard, his assignment depending on (1) his qualifications, (2) his training and expressed preference and (3) the need for men in the different branches of the military.

SELECTIVE SERVICE

As local Selective Service boards now eliminate only the men who are obviously unfit for any type of military service, slight differences exist between minimum requirements and disqualifying visual defects for the Army and for the Selective Service System. The decision at the reception center is final.

SECTION 1.—With regard to functional requirements, local Selective Service boards eliminate only those registrants who are practically blind in both eyes. (See "Functional Requirements" for the Army.)

SECTION 2.—The disqualifying conditions and diseases for any type of military service as determined by the local Selective Service boards are as follows:

1. Lids	Deformity, such as inversion or eversion, of such degree that forcible closure fails to cover eyeball or there is resultant conjunctival inflammation, corneal irritation or a restriction of rotation of eyeball; disfiguring scars; lagophthalmos if associated with signs of hyperthyroidism
2. Orbit	Tumor
3. Muscles	Strabismus, permanent or well marked, of severe degree *
4. Conjunctiva	Disfiguring scars
5. Cornea	Chronic keratitis, severe; chronic ulcer; disfiguring scars
6. Retina and optic nerve	Abnormal conditions of eyes due to disease of brain
7. Miscellaneous	Glaucoma, total blindness

* Strabismus to be disqualifying apparently should be permanent and disfiguring. Local Selective Service boards decide.

SECTION 3.—The regulations supplementing the bibliography given in the original article are contained in the following authority:

Department of Selective Service Form 220, revised Aug. 15, 1942.

ARMY

The physical examinations given at reception centers and directed by the Army are for all branches of the armed forces. The inductee, according to his qualifications and the immediate need of men, is assigned by a special board at the reception center to duty with the Army, Navy, Marine Corps, Coast Guard or Air Corps. WAAC requirements are given under limited service, enlisted and commissioned personnel.

SECTION 1.—The functional requirements for male and female personnel are as follows:

	Vision						Muscles		
	Without Glasses		With Glasses						
	One Eye	Other Eye	One Eye	Other Eye	Refraction	Color Vision	Esophoria	Exophoria	Hyperphoria
A. Enlisted personnel:									
1. General service.....	20/200	20/200	20/40	20/40	Not mentioned in regulations	Color blindness permitted	Not mentioned in regulations		
2. Limited service.....	(*a*) 20/400 (*b*) Loss of eye or blindness not due to progressive organic change	20/400 20/100	20/40 (non-correctable)	20/40 20/20					
B. Commissioned personnel:									
1. General service, all arms and services in Regular Army except Judge Advocate General's Department, Medical Corps and Chaplain Corps	20/40	20/40	20/20	20/30	Not mentioned in regulations	Must distinguish red and green in Holmgren or equivalent test (except Chaplain Corps)	Not mentioned in regulations		
2. Limited service,* Judge Advocate General's Department, Medical Corps, Nurses Corps, Chaplain Corps and all arms and services of the reserve components	20/100	20/100	20/20	20/30					
C. Military Academy:	20/30	20/30	20/20 Not more than 2 D. of hyperopia or 0.75 D. of myopia permitted	20/20	With cycloplegic, +2 D. sph. or less or —0.75 D. sph. or less in each eye	Must distinguish red and green in Holmgren or equivalent test without confusion	Less than— 10 Prism diopter	5	1
* Applicants with the following visual requirements may apply for a waiver from the War Department:	(*a*) Any degree of vision, no organic disease (*b*) Blindness	Any degree of vision, no organic disease 20/200	20/20 Blindness	20/40 20/20	.....	Color blindness permitted			
Commissioned personnel:	Provided there is no organic disease in the better eye and for the more defective eye, no history of cataract or other disease which might be expected to involve the better one, and provided in case of ophthalmosteresis there is a satisfactory prosthesis (*c*) Complete color blindness								

SECTION 2.—The following tabulation indicates under "A" the diseases and conditions which are not disqualifying and under "B" those which are disqualifying.

A. Conditions which are not disqualifying for enlisted personnel, male and female, general and limited service, are as follows:

1. Lids	Slight adhesions to eyeball, blepharitis marginalis if slight, blepharospasm if mild.
2. Lacrimal apparatus	Not mentioned in regulations
3. Orbit	Slight exophthalmos provided hyperthyroidism is excluded
4. Muscles	Nystagmoid movements if not persistent or pronounced and if true nystagmus is excluded, strabismus which does not interfere with vision, ptosis which does not interfere with vision
5. Conjunctiva	Slight conjunctivitis, chronic simple conjunctivitis if mild
6. Cornea	Small pterygium not encroaching on cornea, superficial corneal ulcer provided acceptance is deferred until ulcer is healed without disqualifying impairment of vision
7. Sclera	Not mentioned in regulations
8. Iris and ciliary body	Iridectomy if vision is within minimum standard requrements
9. Lens	Not mentioned in regulations (see visual requirements)
10. Choroid	Not mentioned in regulations
11. Retina	Color blindness
12. Optic nerve and visual portion of brain	Color blindness
13. Miscellaneous	Conditions due to iridectomy or other operation on eye if condition for which operation was performed has been relieved and vision is within or above minimum standard requirements

B. The disqualifying conditions are as follows for:

	(1) Enlisted Personnel, Male and Female, General and Limited Service	(2) Commissioned Personnel, Male and Female, General and Limited Service
1. Lids	Trichiasis; ptosis interfering with vision; disfiguring cicatrices; lagophthalmos if associated with hyperthyroidism; deformity such as inversion or eversion of a degree that (*a*) forcible closure fails to cover eyeball, (*b*) there is a resultant conjunctival inflammation or corneal irritation or (*c*) there is a restriction of rotation of eyeball	Trichiasis, ptosis Disfiguring cicatrices, lagophthalmos Inversion, eversion Extensive destruction of lids, adhesions to eyeball, blepharospasm, chronic blepharitis, malignant tumor
2. Lacrimal apparatus	Chronic dacryocystitis	Chronic dacryocystitis, epiphoria, lacrimal fistula
3. Orbit	Pronounced exophthalmos, tumor	Pronounced exophthalmos, tumor, loss or disorganization of either eye

4. Muscles	Marked nystagmus, permanent or well marked strabismus, diplopia due to paralysis of ocular muscles of one eye *	True nystagmus, permanent or well-marked strabismus, diplopia
5. Conjunctiva	Chronic conjunctivitis, disfiguring cicatrices, trachoma	Chronic conjunctivitis, cicatrices, trachoma
6. Cornea	Chronic keratitis, disfiguring cicatrices, chronic ulcer, trachoma, pterygium interfering with vision, chronic recurrent inflammatory disease of globe	Chronic keratitis, cicatrices, ulcer, trachoma, pterygium encroaching on cornea, opacities encroaching on pupillary area and reducing vision below requirements, staphyloma, xerophthalmos
7. Sclera	Chronic recurrent inflammatory disease of globe	Not mentioned in regulations
8. Iris and ciliary body	Chronic recurrent inflammatory disease of globe	Irregularity in form of iris; extensive coloboma; synechias, anterior and posterior, sufficient to reduce visual acuity below standard; iritis; absence of pigment; tumor
9. Lens	Not mentioned in regulations (see visual requirements)	Opacities reducing vision below requirements, progressive cataract of any degree
10. Choroid	Any active disease	Extensive or progressive disease, extensive coloboma, tumor
11. Retina	Detachment, any active disease	Detachment, retinitis, neuroretinitis, night blindness, tumor
12. Optic nerve and visual portion of brain	Abnormal conditions of eyes due to disease of brain, any active disease	Abnormal conditions of eyes due to disease of brain, neuroretinitis, optic neuritis, atrophy of optic nerve, night blindness, pronounced impairment of color perception
13. Miscellaneous	Glaucoma, vision less than minimum requirements for special and limited military service	Glaucoma, visual functions below requirements, asthenopia accompanying any ocular defect

* Strabismus to be disqualifying should be permanent and disfiguring. Local induction centers decide.

SECTION 3.—The regulations supplementing the bibliography given in the original article are contained in the following authorities:

1. Standards of Physical Examination During Mobilization, Mobilization Regulations 1-9, Oct. 15, 1942, United States War Department: sect. 14, par. 15-20.

2. Medical Department: Standards of Physical Examination for Flying, Army Regulations 40-110, Nov. 16, 1942, United States War Department: par. 16, subpar. 3 (*a*), (*b*) and (*c*); par. 10, subpar. 3 (*b*).

NAVY, MARINE CORPS AND MERCHANT MARINE

SECTION 1.—The functional requirements for enlisted and commissioned personnel, male and female, in the Navy, Marine Corps and Merchant Marine are as follows:

	Vision				Color Vision (Tests Conducted with Pseudoisochromatic Plates for Testing Color Perception; American Optical Company or Stilling Test)
	Without Glasses		With Glasses		
	One Eye	Other Eye	One Eye	Other Eye	
1. Enlisted personnel					
Navy (regular), Marine Corps and Seabees (regular and reserve) except class 4	15/20	15/20	20/20	20/20	Must read one plate of each of the following groups of American Optical Company * plates; (1) plates 1, 2, 3, 4; (2) plates 7, 8, 9, 10, 13, 14, and (3) plates 17, 18, 21, 22 (these groups are represented in Stilling's twentieth edition † by plates 3, 4 and 8
Navy (reserve)	6/20 No organic disease	[Binocular] 15/20	No lens correction necessary		Same requirements as for regular enlisted personnel
Waves	6/20 No organic disease	[Binocular] 12/20	20/20	20/20	
Marine Corps (reserve) class 4 (limited duty within continental United States)‡	8/20	8/20	18/20	18/20	Defective color perception may be waived locally
2. Commissioned officers, line of Navy and Marine Corps	18/20	18/20	20/20	20/20	Must be able to read all pseudoisochromatic plates of American Optical Company or Stilling test
3. Commissioned officers (staff), civil engineers, Supply Corps, Medical Corps, Nursing Corps, Dental Corps and Chaplain Corps; line officers of Reserve Corps doing staff duty as engineers, naval constructors, legal and professional specialists; Seabees and commissioned Waves	12/20	12/20	20/20	20/20	Must complete one of the two tests
4. Naval Academy	20/20	20/20	No myopia or myopic astigmatism with eyes under homatropine cycloplegia		Must complete one of the two tests
5. Enlisted reserve (potential officers):§	....	....	....	....	Must complete one of the two tests ‡
Class V1-G	18/20	18/20	20/20	20/20	
Class V1-S	12/20	12/20	20/20	20/20	
Class V5	20/20	20/20			
Class V7-G	18/20	18/20	20/20	20/20	
Class V7-S	12/20	12/20	20/20	20/20	
6. Merchant Marine class M1, M2	Same requirements as for enlisted reserve personnel				

* American Optical Company: Pseudo-Isochromatic Plates for Testing Color Perception, Southbridge, Mass., American Optical Company, 1940.

† Stilling, J.: Stillings pseudo-isochromatische Tafeln zur Prüfung des Farbensinnes, ed. 20, Leipzig, G. Thieme, 1939.

‡ Defective color perception may be waived locally for the Sp. (S) rating and for the construction regiment in class V6. Defective vision and defective color perception may receive special consideration for the Sp.(O) and the Sp. (T) rating of class V6.

§ The classes of the United States Naval Reserve are as follows: V1-G, V1-S, enlisted college students, inactive reserve; V3, 4 and 6, enlisted reserve; V5, aviation cadets; V7-G, V7-S, enlisted midshipmen; V9, women enlisted as apprentice seamen for training preliminary to appointment as midshipmen and further training for commissions; V10, women enlisted for service in the naval establishment ashore; W-V (S), commissioned officers in the Women's Reserve; M1, enlisted personnel for transoceanic service in the Merchant Marine; M2, enlisted personnel for inshore or coastal patrol in the Merchant Marine, and Marine Corps class 4, limited duty, guard duty in the United States only.

SECTION 2.—The disqualifying conditions and diseases for enlisted and commissioned personnel are as follows:

1. Lids	Destruction of lids, disfiguring cicatrices, adhesions, inversion, eversion, lagophthalmos, trichiasis, ptosis, blepharospasm, chronic blepharitis, malignant tumor
2. Lacrimal apparatus	Epiphoria, chronic dacryocystitis, lacrimal fistula
3. Orbit	Loss or disorganization of one eye, pronounced exophthalmos
4. Muscles	Pronounced nystagmus, marked strabismus, diplopia
5. Conjunctiva	Cicatrices, chronic conjunctivitis, trachoma
6. Cornea	Chronic keratitis, ulcer, staphyloma, opacities, reducing vision below requirements, cicatrices, pterygium, trachoma, xerophthalmos
7. Sclera	Not mentioned in regulations
8. Iris, ciliary body	Irregularities in form of iris, coloboma, iritis, albinism, tumor
9. Lens	Opacities reducing acuity of vision
10. Choroid	Choroiditis, coloboma, tumor
11. Retina	Retinitis, neuroretinitis, detachment of retina, night blindness, tumor
12. Optic nerve, visual part of brain	Neuroretinitis, optic neuritis, atrophy of optic nerve, night blindness, abnormal conditions of eye due to diseases of brain
13. Miscellaneous	Glaucoma, asthenopia, visual functions below requirements

SECTION 3.—The regulations supplementing the bibliography given in the original article are contained in the following authorities:

1. Physical Examination for the Medical Department of the United States Navy, reprint of chapter 11, Manual of the Medical Department, 1938: par. 1401-1407 and 1426-1432. (General.)
2. Recruiting Circular Letter 124-42, Nov. 13, 1942, United States Navy Department: par. 1. (Navy, regular.)
3. Letter of Instruction 54, Dec. 8, 1941, United States Navy Department: par. 4-6. (Marine Corps, regular and reserve.)
4. Recruiting Circular Letter 110-42, Aug. 24, 1942, United States Navy Department: enclosure C, par. 1 and 3 (*c*). (Navy, reserve.)
5. Letter of Instruction 246, Nov. 4, 1942, United States Navy Department. (Marine Corps, reserve, class 4.)
6. N-O-P-C-L 29-42, July 23, 1942, United States Navy Department. (Enlisted Waves; V10.)
7. ARL 530 TWX OP 9-30-11 45/NR, United States Navy Department. (Enlisted Waves; V10.)
8. Recruiting Circular Letter 36-42, Feb. 21, 1942, United States Navy Department. (Specialist ratings; Seabees.)
9. Recruiting Circular Letter 127-42, Nov. 20, 1942, United States Navy Department: enclosure E, par. 1 (*b*), (Sp.O); enclosure H, par. 3 (Sp.S); enclosure I, par. 3 (Sp.T).

COAST GUARD

SECTION 1.—The functional requirements for the Coast Guard are as follows:

	Vision				
	Without Glasses		With Glasses		
	One Eye	Other Eye	One Eye	Other Eye	Color Vision
1. Applicants for enlistment.....	20/30	20/30	20/30	20/30	Normal color vision required
2. Cadets for appointment as ensigns Candidates for original commissions as constructors, district commanders or chief warrant officers	20/30	20/30	20/20	20/20	Normal color vision required: "Color perception will be tested by the colored plate test in accordance with the instructions contained in Hospital Division Circular 255 (authority 3)
3. Candidates for appointment as cadets	20/20	20/20	20/20	20/20	Normal color vision required
4. Spars.....	The visual requirements for enlisted and commissioned personnel are the same as those for enlisted and commissioned Waves				

For reserve personnel the following regulations concerning waivers may be considered:

Uncorrected vision of 20/40 in one eye, with 20/20 in the other eye, may be waived; uncorrected binocular vision of not less than 20/40, with vision of not less than 20/70 in the worse eye, may be waived if each eye is corrected to 20/30 or better.

Applicants who read correctly 75 per cent of the plates of the Ishihara or pseudoisochromatic test for color perception should not be rejected for defective color perception. Defective color perception may be waived for all ratings other than those of the seaman branch and pharmacist's mate. In the cases of officer applicants defective color perception may be waived for those assigned to engineering duty or special duty. Defective color perception will not be waived for officer candidates who may at any time be assigned to duty on deck.

No waivers in the regular corps, commissioned and enlisted personnel, will be accepted.

SECTION 2.—The disqualifying conditions and diseases are the same as those for the Army and Navy.

SECTION 3.—The regulations supplementing the bibliography given in the original article are contained in the following authorities:

1. Instructions for Medical Officers Relative to Physical Examinations, United States Coast Guard, 1943,
2. United States Coast Guard Personnel Bulletin 104-42, Oct. 29, 1942.

AIR CORPS: ARMY AND NAVY

Physical examinations in all branches of the Air Corps are given only by specially trained and qualified examiners. This section has, therefore, been condensed because of its limited use to the majority of readers.

SECTION 1.—Air Corps ophthalmic requirements in the Army and in the Navy, which includes the Marine Corps and the Coast Guard, are basically similar. Specific differences are detailed in the following tabulation, which combines the functional requirements of all branches of the Air Corps and classifies them into four groups.

GROUP I

A. Classification of personnel

1. Army, class 1.
   - (*a*) Applicants for flying training
   - (*b*) Rated senior pilots
   - (*c*) Pilots
   - (*d*) Combat observers
   - (*e*) Balloon pilots
   - (*f*) Senior balloon pilots
   - (*g*) Balloon observers

2. Navy

   Class 1, pilots
   - (*a*) Pilots with less than twenty years of service
   - (*b*) Pilots with twenty to thirty years of service; same requirements as given hereafter except that vision must be 10/20 in each eye without glasses and 20/20 in each eye with glasses
   - (*c*) Pilots with thirty years or more of service; same requirements as given hereafter except that vision must be 8/20 in each eye without glasses and 20/20 in each eye with glasses

   Class 2, other flying personnel
   - (*a*) Student naval aviators
   - (*b*) Naval aviators (airship)
   - (*c*) Student naval aviators (airship)

   Class 3, nonflying personnel
   - (*a*) Naval aviator observers
   - (*b*) Naval flight surgeons
   - (*c*) Student naval flight surgeons (vision without glasses 15/20 in each eye)
   - (*d*) Antiaircraft and aircraft machine gunners

B. Functional requirements for class 1 of Army and classes 1 to 3 of Navy

Vision without glasses (glasses not permitted): each eye 20/20

Refraction with a cycloplegic will not be done as a routine procedure but will be done when deemed necessary by the examiner (Army) and must show

Army: each eye less than + 1.5 D. sph. or + 0.5 or — 0.5 D. cyl.

Navy: each eye less than + 2.0 or — 0.5 D. sph. or + 0.5 or — 0.5 D. cyl.

Field of vision: less than 15 degrees of contraction in any meridian

Color vision: completion of Ishihara or Stilling test

Depth perception: at 6 meters, 30 mm. limit (Howard-Dolman apparatus)

Muscles, extrinsic

Heterotropia, none

Esophoria

1. Less than 10 prism diopters
2. Less than 4 prism diopters when associated with prism divergence less than 4 prism diopters

Exophoria: Less than 5 prism diopters

Hyperphoria: Less than 1 prism diopter

Fusion power:

(*a*) Power of convergence: the distance from the base line to the near point of convergence (PcB) must not exceed interpupillary distance by more than 25 mm.

(*b*) Power of divergence (prism divergence)

1. This test is accomplished with the spotlight at 20 feet (610 cm.) and with prisms placed immediately in front of the eyes
2. A power of divergence of more than 15 or less than 3 prism diopters disqualifies; when esophoria exists, the prism divergence in diopters must be equal to or greater than the diopters of esophoria

(*c*) Field of binocular rotation (red lens test)

(1) The primary position is a point 75 cm. directly in front and on a level with both eyes

(2) When diplopia occurs within 27.3 cm. of the primary position, the test will be completed by recording on a tangent screen or blackboard the exact points at which it occurs; the distance from the primary point at which diplopia first occurs will be measured in centimeters

(3) Diplopia within 50 cm. in any meridian disqualifies; for command and service pilots diplopia within 27.3 cm. in any meridian disqualifies

GROUP II

Accommodation: less than 3 D. below normal for age

A. Classification of personnel

Army, class 2

(*a*) Rated senior pilots

(*b*) Pilots

(*c*) Combat observers
(*d*) Balloon pilots
(*e*) Senior balloon pilots
(*f*) Balloon observers, provided their training and experience in the opinion of the chief of the Air Corps compensates for the lower physical standards of class 2

B. Functinal requirements for class 2 of Army Vision without glasses: each eye 20/40
Vision with glasses: each eye 20/20
Refraction: same as Army, class 1
Field of vision: same as Army, class 1
Color vision: same as Army, class 1
Depth perception: at 6 meters, 35 mm. limit (Howard-Dolman apparatus)
Muscles and fusion power: same as Army, class 1
Accommodation: not less than 3 D. absolute; glasses for near vision may be required for flying; ability to read test at 50 cm.

GROUP III

A. Classification of personnel
Army, class 3
(*a*) Rated command pilots
(*b*) Technical observers
(*c*) Officers of other arms and services detailed by competent authority to duty involving flying

B. Functional requirements for class 3 of Army: same as for class 1 except
Vision without glasses: each eye 20/100
Vision with glasses: each eye 20/20
Depth perception: not required, except for command pilots (at 6 meters, 35 mm. limit)
Muscles, extrinsic
Heterotropia: none
Esophoria: less than 12 prism diopters
Exophoria: less than 7 prism diopters
Hyperphoria: less than 2 prism diopters
Fusion power: tests omitted
Accommodation: glasses for near vision may be required for flying; ability to read test at 50 cm.

GROUP IV

A. Classification of personnel: ground crews

B. Functional requirements for ground crews: same as for general military service, enlisted personnel, Army and Navy

Muscle imbalance beyond the qualifying limits for classes 1, 2 and 3 may be waived in the case of aviation cadets applying for or undergoing training as navigators and rated navigators, provided binocular single vision is maintained in the primary position and in all the cardinal directions of vision; aviation cadets undergoing training as navigators and rated navigators may be qualified in class 2 with a waiver regardless of the amount of correction required to give vision of 20/20

SECTION 2.—The disqualifying conditions and diseases for all classes or groups of the Army and the Navy Air Corps are as follows:

1. Any defect of a permanent nature materially interfering with the normal functions of the eye

2. The disqualifying conditions and diseases enumerated in the tabulations for the Army and the Navy

SECTION 3.—The regulations supplementing the bibliography given in the original article are contained in the following authority:

Medical Department: Standards of Physical Examination for Flying, Army Regulations 40-110, Dec. 3, 1942, United States War Department: sect. 3, par. 11-17.

UNITED STATES PUBLIC HEALTH SERVICE

SECTION 1.—The minimum functional requirements for the United States Public Health Service are as follows:

	Vision				
	Without Glasses		With Glasses		
	One Eye	Other Eye	One Eye	Other Eye	Color Vision
Candidates for appointment in the commissioned corps	20/40	20/70	20/20	20/40	Normal; tested with colored plates

SECTION 2.—As to disqualifying conditions and diseases, any chronic disease of the visual organs is sufficient for rejection.

SECTION 3.—The following authority is cited:

Regulations for Government of Public Health Service, United States Treasury Department, 1931.

MISCELLANEOUS INFORMATION

In the Navy, vision is expressed as a fraction, of which the numerator is the distance at which Snellen's 20 foot (610 cm.) test letters can be determined and the denominator is 20 when vision is defective or normal. When vision is better than normal, the denominator shall be 15 or 10 as the case may be. Thus 20/20 indicates normal vision, 15/20 less than normal and 20/15 better than normal.

In the Army, vision is expressed as a fraction of which the numerator is always 20 and the denominator the lowest readable line of the Snellen chart.

The importance of verifying vision in the military service must not be underestimated. A simple method is to use any 20 foot letter for all persons with subnormal vision, having the examinee approach until he can call an unknown letter. For further verification use slightly larger or smaller letters. Thus a person with a vision of 20/40 in one eye would have to come to 10 feet (305 cm.) to distinguish a 20 foot letter. He would also see the 30 foot (914 cm.) letter at approximately 15 feet (457 cm.) and the 15 foot letter at approximately 8 feet (244 cm.). Obviously, the test letter or figure should be jet black on a clean white background and have a luminosity of approximately 10

to 15 foot candles. The examinee should have the untested eye completely occluded without pressure.

The following tests for malingery and exaggeration are described in "Standards of Physical Examination During Mobilization, Mobilization Regulations 1-9" (United States War Department, Aug. 31, 1940) section 4, paragraphs 19 and 20: examination with the (1) stereoscope, (2) bar, (3) mirror, (4) prism, (5) colored lens and (6) trial glass and (7) examination of the pupils.

The technics which are now used in testing visual acuity and were not mentioned in the previous article are given in the following authorities:

1. Medical Department: Standards of Miscellaneous Physical Examination, Army Regulations 40-100, Nov. 16, 1942, United States War Department.

2. Medical Department: Standards of Physical Examination for Flying, Army Regulations 40-110, Dec. 3, 1942, United States War Department.

The taking of visual fields is required only when indicated by the results obtained with finger and fixation tests.

"Conditions and diseases not mentioned in the regulations previously mentioned and which may cause disqualification of the selectee are to be looked for and recorded by the examining physician" ("Selective Service Regulations," United States Selective Service System, 1940, vol. 6, par. 606).

Diseases of a selectee reportable by law must be reported to the civil authorities through the proper channels ("Selective Service Regulations," United States Selective Service System, 1940, vol. 6, par. 614-615).

The visual tests involved in reexaminations have not been changed since publication of the original article.

CONCLUSION

In conclusion: I will appreciate being advised of inaccuracies and ambiguities observed by readers.

This revision was made possible through the cooperation of Brigadier General James C. Magee, surgeon general, United States Army; Rear Admiral Ross T. McIntire, surgeon general, United States Navy, and Surgeon General Thomas Parran, United States Public Health Service. The following persons were of assistance: Lieutenant Colonel Cornelius E. Gorman, Medical Corps, United States Army; Lieutenant Commander J. E. Fulghum, Medical Corps, United States Naval Reserve; Major F. P. Rizzo, Medical Corps, United States Army; Assistant Surgeon W. H. Stimson, United States Public Health Service; Dr. Frank F. Thweatt Jr., assistant chief, Hospital Division, United States Public Health Service; Captain Eugene Countiss, United States Public Health Service; Dr. E. Schmerl; Dr. J. I. Pascal; Miss Claire Wichser, and Mrs. E. C. Ferrell.

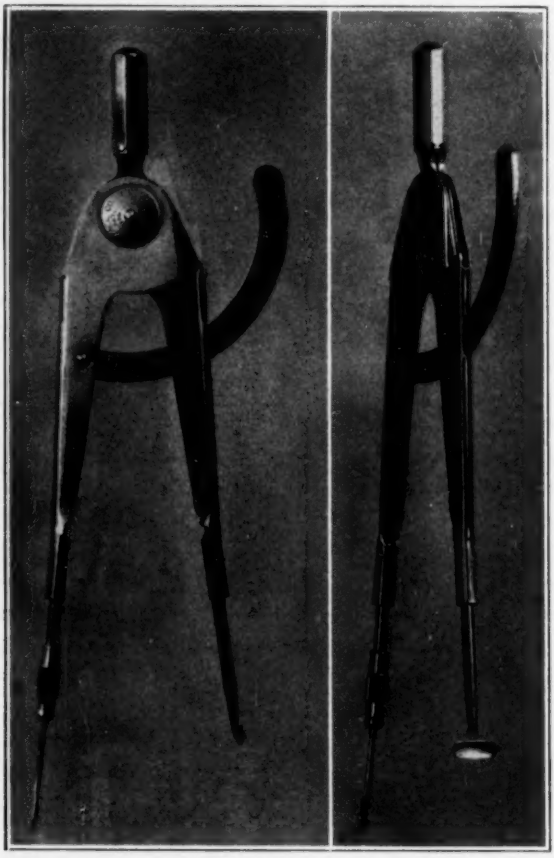
1703 Pere Marquette Building.

Correspondence

IMPROVISED EXOPHTHALMOMETER

To the Editor:—I herewith submit a description and an illustration of an improvised exophthalmometer.

The instrument is inexpensive. An ordinary compass is used, and to the movable leg is added a grooved cross piece, the lateral rim of the orbit fitting into the groove. To the fixed leg is added a spatula which extrudes beyond the plane of the shorter leg by 18 mm.



The patient's eye is anesthetized before the instrument is used. While the patient looks straight ahead, the groove on the cross piece attached to the shorter leg is placed on the lateral rim of the orbit, and the longer leg is brought just up to the center of the cornea. The reading on the protractor scale in degrees is multiplied by three. This gives the amount of proptosis expressed in millimeters.

The readings obtained with this instrument have been compared with those obtained with a Hertel exophthalmometer and have been found to agree.

EDWARD S. MURPHY, Lieutenant Colonel, M.C., A. U. S.

News and Notes

EDITED BY DR. W. L. BENEDICT

UNIVERSITY NEWS

de Schweinitz Library Hospital of the University of Pennsylvania.—The recent opening of the de Schweinitz library in the University of Pennsylvania marked the inauguration of a memorial to Dr. George Edmund de Schweinitz, who was professor of ophthalmology at the University of Pennsylvania from 1902 until 1924.

The library is a room approximately 20 by 40 feet, paneled in birch with a natural finish. At one end is a splendid portrait of Dr. de Schweinitz, done by Seyffert and presented to the medical school by the medical class of 1925. This portrait was fitted into the paneling of the wall, and the whole room was built around this portrait as a pivotal point. The library contains approximately 2,500 volumes.

The library is designed for the use of all physicians and students of ophthalmology.

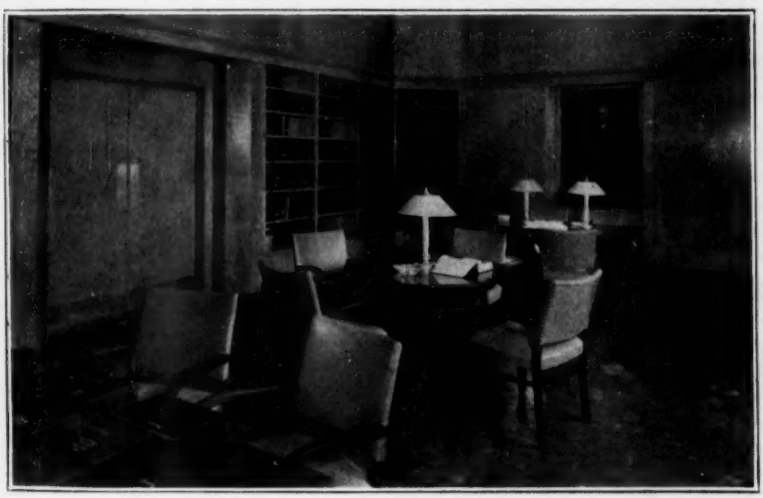


Fig. 1.—View of the library showing the portrait of de Schweinitz.

Fig. 2.—Another view of the de Schweinitz library.

SOCIETY NEWS

Medical Society of the State of New York.—The Section on Ophthalmology and Otolaryngology met May 5 at the Hotel Statler. The following papers were presented: "Bilateral Uveitis with Poliosis, Vitiligo, etc.—A Theory as to Cause," Dr. Eliott B. Hague, Buffalo, with discussion by Dr. Thurber Le Win, Buffalo; "Epidemic Keratoconjunctivitis," Dr. Arthur J. Bedell, Albany, with discussion by Major Murray Sanders Medical Corps, Army of the United States; "Gas Injuries," Dr. Francis Heed Adler, Philadelphia, with discussion by Dr. Alson E. Braley, New York; "Early Recognition and Management of Glaucoma," Dr. Harry S. Gradle, Chicago, with discussion by Dr. Algernon B. Reese, New York, and "Corneal Diseases with Lowered Vitality," Dr. Ralph I. Lloyd, Brooklyn, with discussion by Dr. Arno E. Town, New York.

Association for the Prevention of Blindness in Mexico City.—In celebration of the twenty-fifth anniversary of its founding, this association will hold a scientific week from August 13 to 21. The week will be a memorable event for Mexican ophthalmologists.

Obituaries

CHARLES WADHAMS STEVENS, M.D.
1868–1943

Dr. Charles Wadhams Stevens died suddenly at his home in New York on March 15, 1943. He was 75 years of age.

He was the son of Dr. George T. Stevens. The elder Stevens was one of the outstanding ophthalmologists of his time. Graduated in a period when medical education was rudimentary, he served three years as an army surgeon during the Civil War, and when peace came he decided to specialize in ophthalmology. For the last forty years of his long life he restricted his practice to the motor anomalies of the eyes, a new subject, in which he was a pioneer and in which he made a world-wide reputation. His classification and nomenclature had remained practically unchanged to this day. He was the father of the "phorias" and the "tropias" and of the "graduated tenotomy" and numerous other operations on muscles. His name is attached to numerous ingenious scientific instruments to determine the position and movements of the globe. The phorometer, the tropometer and the clinometer all were his. He designed many delicate operating instruments which are still unsurpassed, and his operative skill was unexcelled. On the clinical side he evolved theories of muscular imbalance and incoordination and their profound effects on health and function which were savagely disputed by many of his colleagues and involved him in controversies which he made no effort to evade. He published a long list of books and pamphlets and was known all over the world.

Charles Stevens graduated from Princeton in 1889 and received his medical degree from Columbia in 1892. Afterward he studied abroad at Edinburgh and at Jena. For many years he was his father's assistant and associate, and finally he inherited an office practice so large and so time consuming that it left scant opportunity for hospital work or contact with other ophthalmologists or schools of thought. He was a firm and loyal believer in his father's theories and was a dexterous operator in his chosen field.

He was a real scientist and perfectly competent to defend his beliefs, but he was a kindly, modest man who heartily disliked controversy. He wrote comparatively little and pushed himself not at all. He was one of the early experimenters with roentgen rays, collaborating with Pupin in this work. He was a skilled photographer and attempted to photograph the fundus long before there were adequate plates and cameras. He

was a botanist like his father before him, an ornithologist of distinction and a real musician.

During the Spanish-American War he served his country as an assistant surgeon, and during World War I he was a member of the medical advisory board organized at the New York Post-Graduate Hospital. Afterward he was an instructor in its medical school, devoting himself chiefly to physiologic optics, which interested him keenly. He was a good and a popular teacher.

During the last years of his life his health failed and he gradually withdrew from practice, devoting himself to his home, his church, his books and his music. In 1917 he had married Marion Paine, who shared many of his pursuits and pleasures and helped make his life a happy and a useful one.

ELLICE M. ALGER.

W. HOLBROOK LOWELL, M.D.

1875–1943

Dr. William Holbrook Lowell was born in Halifax, Nova Scotia, Canada, April 8, 1875, while his parents, natives of Maine, were temporarily in that city. He died March 31, 1943, in Winchester, Mass., of a recurrent coronary obstruction. He was a lineal descendent of James Russell Lowell.

He entered Harvard in 1894 but was forced to leave college because of severe typhoid fever. He spent a year in foreign travel and then entered Harvard Medical School, graduating in 1902. He was intern at the Boston City Hospital and the Massachusetts Eye and Ear Infirmary. He went through all the grades up to consulting ophthalmic surgeon at the Massachusetts Eye and Ear Infirmary. He also served on the staff of the Boston City Hospital, Boston Dispensary, Children's Mission and Lincoln House, and as consulting ophthalmic surgeon at the Massachusetts General Hospital, the Lawrence Memorial Hospital, in Medford, Mass., and the Lawrence General Hospital, in Lawrence, Mass. He taught many years in the Harvard Graduate School of Medicine.

During the first World War, he was a member of the Medical Advisory Board of Massachusetts. He was certified by the American Board of Ophthalmology in 1920. He was a member of the American Medical Association, American Ophthalmological Society and American Academy of Ophthalmology and Otolaryngology and of the New England Ophthalmological Society, of which he was president in 1928. For many years he was an associate examiner for the National Board of Medical Examinations.

In 1904 he married Marion Isabel Symington, of Windsor, Ontario, Canada. They had two children—a daughter, married to Dr. Edward S. Stafford, of Baltimore, now a major in the Army Medical Corps, on duty somewhere in the South Pacific, and a son, Dr. W. Holbrook Lowell Jr., who is a captain in the Army Air Corps, Medical Unit, now stationed in Tennessee. There are six grandchildren.

Dr. Lowell published about a dozen papers. He was particularly interested in operations on the muscles and in subconjunctival cataract extraction. He devised the red and green lines on the Snellen chart. Long after it is forgotten who was the inventor, this simple but ingenious device will be widely used. He won the good will and friendship of a host of medical men, for he was a kindly, generous, cooperative and unassuming gentleman.

WALTER B. LANCASTER.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

EPIDEMIC KERATOCONJUNCTIVITIS. M. L. BERLINER, Am. J. Ophth. **26:** 50 (Jan.) 1943.

Berliner gives a brief historical outline and describes epidemic keratoconjunctivitis as characterized by sudden onset, as though produced by a foreign body, and by excessive lacrimation and marked edema. On the second or third day there is swelling of the preauricular glands, which may or may not be painful and generally subsides in a week. In the first few days secretion is minimal, but later it may become profuse, and dirty gray membranes may form. More than half the patients complain of blurring when the acute symptoms subside. This results from small discrete grayish infiltrates in the pupillary area in Bowman's zone. Beginning in December 1941 Berliner observed 18 cases, the general characteristics of which he describes. He states that the lesions may not be specific and that bacteriologic studies by separate workers have given uniformly negative results. Therapy is of little value, cold compresses and a weak solution of sodium bicarbonate giving some relief.

W. S. REESE.

HITHERTO UNDESCRIBED DEGENERATIVE CHANGE OF CORNEA: REPORT OF A GENEALOGY. W. REICHLING, Klin. Monatsbl. f. Augenh. **105:** 324 (Sept.) 1940.

Reichling describes the corneal condition of 2 sisters, the incestuous offspring of a father and his illegitimate daughter. The father was a criminal psychopath, and many degenerative signs occurred in the family. The corneas of the two girls presented about the same aspect. The substantia propria was dotted with countless yellowish spots. Aside from these, larger, superficially located spots were visible in a circular arrangement at a certain distance from the corneal center. The larger spots were grayish white and prominent above the level of the cornea; the largest were the most prominent. Most of the spots were found at the lower portion of the ring; they did not extend into the deeper layers of the cornea. Centrally to the row of these spots a narrower pigmented line was observed between 3 and 7 o'clock. The iris appeared to be normal, and no remnants of inflammatory origin or newly formed blood vessels were present. In the second patient two symmetric and concentric rings of whitish gray opacities existed instead of only one. The opacities were limited to the surface. Reichling considered these changes as hereditary dystrophies of a special type, as they could not be classified with either one of Bückler's types.

K. L. STOLL.

Experimental Pathology

GENUINE TETANIC NUTRITIONAL CATARACT. G. BIETTI, Klin. Monatsbl. f. Augenh. **105:** 299 (Sept.) 1940.

The author refers to the divers forms of nutritional cataract, described by a number of writers and compiled by Jess, and reports on his research with different types of nutrition in rats. The cataract produced was identical with the spontaneous cataract observed in rats. It developed in 80 to 90 per cent of 120 rats. Tables and photomicrographs serve as illustrations.

Bietti concludes that long-lasting and latent nutritional tetany accompanied by cataract may be produced independently from rachitis by means of a diet poor in calcium as compared with phosphorus and lacking calcium-fixing vitamin D. The diet should contain calcium and phosphorus in a ratio of not more than 1 : 4, with a calcium level not exceeding 0.040 per cent. In rachitic animals even a smaller disturbance of the calcium and phosphorus ratio will produce cataract, although it does not occur so constantly. An increased phosphorus content in the diet will further to some extent the formation of cataract, which is accompanied by increased neuromuscular irritability and distinct hypocalcemia. The artificial cataract he produced represents a new type, namely a purely tetanic nutritional form, independent from rachitis. The experiments, in Bietti's opinion, are a contribution to the etiology of nutritional cataracts, and in addition the simplicity and reliability of the method of research makes it readily adapted to experiments on opacification of lens fibers and on cataract in general. The difficulty of experimenting with the small eyes of rats may in due time be overcome through use of larger animals.

K. L. STOLL.

Glaucoma

PROSTIGMINE IN THE TREATMENT OF GLAUCOMA: ITS EFFECT ON INTRAOCULAR PRESSURE. P. MONTALVÁN, Am. J. Ophth. **26:** 57 (Jan.) 1943.

Montalván gives five tables showing the results of his studies and draws the following conclusions:

"1. Prostigmine has proved to be a valuable addition to the armamentarium of the ophthalmologist in the treatment of glaucoma—notably in the chronic primary type.

"2. In an appreciable percentage of cases initially controlled with the 5-percent solution of prostigmine bromide, it has been found that the 2½-percent solution can be satisfactorily substituted. It is recommended that this procedure be adopted whenever possible in the interests of comfort and economy.

"3. Subjectively, prostigmine seems to interfere less with the normal use of the eyes in the patient's daily routine, as compared with other miotics."

W. S. REESE.

Lacrimal Apparatus

DACRYOCYSTORHINOSTOMY FOR CHRONIC PURULENT DACRYOCYSTITIS WITH POSITIVE BACTERIOLOGIC OBSERVATIONS: REPORT OF CASES. D. LUKIĆ, Klin. Monatsbl. f. Augenh. **106:** 291 (March) 1941.

Lukić obtained satisfactory results in chronic purulent dacryocystitis by flushing the tear sac with antiseptic and other solutions, such as optochin hydrochloride or 2,ethoxy-6,9-diaminoacridinium hydrochloride (rivanol) after bacteriologic examination of pus taken from the tear sac. After the secretion ceased and the bacteriologic examination of the secretion gave negative results, he performed dacryocystorhinostomy according to the method of Ohm, Dupuy and Dutemps or that of Toti. In cases of persisting, stubborn suppuration or in the presence of an ectatic tear sac the operation in two stages according to the method of Nižetić was employed. Nižetić's method, however, consumes more time for recovery than Lukić's. In the latter pus flows into the wound, but it does not cause infection, probably, in the author's opinion, because of immunization created during protracted purulent inflammation. One advantage of Lukić's method is that the pus drains into the patient's nose instead of through an outside fistula. Lukić obtained prompt healing in 7 cases, with free passage through the tear apparatus in seven to thirteen days.

K. L. STOLL.

Neurology

AMAUROTIC FAMILY IDIOCY. J. H. GLOBUS, J. Mt. Sinai Hosp. **9:** 451 (Nov.-Dec.) 1942.

Globus gives a brief historical review of amaurotic family idiocy and presents brief clinical histories and detailed anatomic observations on 12 cases of the infantile form (in 1 case the disease was combined with Niemann-Pick disease) and 1 case of the juvenile form. The clinical and anatomic features of the late infantile, adult and congenital forms are described, and their relation to the entity is discussed. New observations on the ubiquity of the disease process include the disclosure that isolated cell groups outside the central nervous system exhibit alterations characteristic of the disease. Changes in the posterior lobe of the pituitary are advanced, and the numerous globoid granular bodies found there are unusually large. The several forms of the disease, including one which is associated with Niemann-Pick lipid histiocytosis, belong to a single disease entity characterized by a disturbance in lipid metabolism. Too great emphasis has been placed on focal variations in the intensity of the pathologic process as observed in the several variants of the disease. A study of the endocrine organs in several of the cases which the author reports failed to provide evidence supporting the view that their dysfunction is at the base of the disease process. The presence of nerve cell groups within the territorial domain of some glands of internal secretion (adrenal, posterior lobe of the pituitary body) is thought by him to be no more than an item in the ubiquitous disease process, which universally affects nerve cells. The general conclusion is that amaurotic family idiocy is a malformation characterized by defective constructive material in the affected cells or by the

cells' lack of capacity for assimilating available material. Either of these difficulties is capable of causing regressive morphologic changes resulting in dysfunction and finally in total disintegration of the affected cells.

J. A. M. A. (W. ZENTMAYER.)

Refraction and Accommodation

CORNEAL SCARS AND MYOPIA: REPORT OF CASES. D. A. TODOROFF, Klin. Monatsbl. f. Augenh. **105:** 561 (Nov.) 1940.

The author examined 52 patients with myopia and corneal scars with a view to demonstrating a connection between these two conditions. He reports 11 of their histories briefly. He found myopia in about three fourths. The injury causing the corneal scars may involve other parts of the anterior segment of the eyeball, especially the ciliary muscle and the lens. Spasm and paresis of the accommodation after an injury may result in contraction or atrophy. Refractive myopia may develop, which will remain in adults but change to axial myopia in children. The younger the child, the greater the progress of myopia. Hyperopia may result from a hard blow on the eye. Hereditary tendencies may exert some influence on the development of myopia in the presence of corneal scars after an injury.

K. L. STOLL.

MY EXPERIENCES IN AMERICA AND THE QUESTION OF MYOPIA. E. NOWAK, Klin. Monatsbl. f. Augenh. **105:** 575 (Nov.) 1940.

Lindner's theory of the origin of myopia revived the topic of myopia, which had been dormant for many years. Nowak reports on his experiences during seventeen years of ophthalmologic practice in Iowa. He discusses his findings in the light of the theory of a hereditary disposition to myopia. Such a disposition, he concludes, does not exist. He is rather inclined to relate many of his findings to Lindner's ideas. Americans consult the oculist and optometrist more frequently for minor refractive errors than the people of Vienna, where he has been practicing since 1939. Hyperopic patients far exceed myopic patients. The idea of so-called school myopia, in Nowak's opinion, is incorrect. He found that American children read more at home than European children, which would compensate for the more strenuous school work of the European children. More favorable living conditions in America play an important role. Children of myopic immigrants, born in this country, showed a predominant percentage of hyperopia and hyperopic astigmatism. Systematic examination of school children, as well as in his own practice, showed that myopia in children under 10 years amounted to less than 0.25 per cent. Myopia was even less frequent among the second and third generation born in this country. In Iowa sometimes a week passed during which Nowak saw no new myopic patient, whereas after his return to Vienna hardly a day passed without one. Mutation by adaptation is of greater importance in reducing the percentage of myopia than heredity in preserving it. The author refers to several highly myopic couples whose children (nine children in one instance) were hyperopic; most were slightly so but one had a high

degree of hyperopic astigmatism. Nowak agrees with Lindner that progressive myopia is due to a pathologic condition, independent of a hereditary tendency but caused by postnatal lesions of the posterior segment of the eyeball. He disagrees with Steiger, who maintains that extrinsic lesions exert no influence on the origin or progress of myopia. Nowak is much in favor of advising the myopic youth to choose an occupation suited to his ocular condition.

K. L. STOLL.

Retina and Optic Nerve

ADHESION OF VITREOUS TO RETINA IN DETACHMENT OF RETINA: REPORT OF CASES. J. BÖCK, Klin. Monatsbl. f. Augenh. **105:** 276 (Sept.) 1940.

Clinical and anatomic research point to detachment of the retina and formation of retinal tears as being preceded by changes in, and detachment of, the vitreous. Leber and Nordenson found that shrinkage of the vitreous produces its separation from the retina. Gonin demonstrated that adhesions between vitreous and retina produce holes in the latter. Best and other writers showed that motion of the eyeball causes shifting of the vitreous, thus producing holes in the retina, with consecutive detachment of the retina. Histologic research led some writers to disagree with these findings, which are supported by observations by Böck on 2 patients, a woman aged 65 and a man aged 57. The essential symptoms were similar. Both patients were highly myopic and had multiple tears in the retina located sufficiently central for examination with Lindner's vitreous microscope under slit lamp illumination, although the retina was far removed from its substratum. The vitreous was clear enough to permit exact observation, the result of which supported clinically the anatomic finding that in most instances of detachment of the retina the vitreous is connected with the lid of the retinal hole. The adhesions of vitreous and edge of the hole or lid, therefore, are not artefacts, as they existed before the hardening of the enucleated eyeball. Hence this condition represents the result of a pathologic process.

K. L. STOLL.

TUBERCULOUS CAUSATION OF PERIPHLEBITIS OF RETINA. E. WERDENBERG, Klin. Monatsbl. f. Augenh. **105:** 285 (Sept.) 1940.

The author discusses the views of two opposing groups of authors of the cause of periphlebitis of the retina. Referring to the views of Axenfeld and his followers, who favor a tuberculous origin, he presents clinical, pathologic-anatomic and experimental reasons. Evaluating the ideas of von Hippel and Bürger, who also support this theory, he disagrees with Marchesani, who is of the opinion that thromboangitis obliterans is the cause of this disease. Basing his view on the large clinical material of Davos, Werdenberg concludes as follows: 1. A logical connection between periphlebitis of the retina and intrathoracic tuberculosis exists in a large percentage of cases. 2. In a considerable percentage of cases there exists inflammatory involvement of the iris and choroid of an actual or suspected tuberculous nature. 3. The satis-

factory clinical results obtained in a large number of unfavorable cases in which treatment was directed at a tuberculous disease speak for frequency of a tuberculous origin of periphlebitis. Focal reactions to treatment for tuberculosis were considered as an undesired but positive therapeutic proof of the tuberculous causation. The tuberculous origin of periphlebitis of the retina in most cases appears to be established. Wardenberg, therefore, sees no reason for discontinuing the therapy adopted after decades of research in this disease. It is the duty of the physician, he states, to adhere to established therapeutic principles in the treatment of this malignant ocular disease, with its threat of imminent blindness.

K. L. Stoll.

Preretinal Hemorrhage with Cerebral Hemorrhage: Report of Cases. H. Davids, Klin. Monatsbl. f. Augenh. **105:** 549 (Nov.) 1940.

Davids reports 2 cases of retinal hemorrhages accompanying cerebral hemorrhages. The first patient, a man aged 30, suffered a cerebral hemorrhage with unconsciousness, paralysis of the right arm and right leg and facial paresis on the same side. A large preretinal garland-shaped hemorrhage in the macular region of the left eye was observed. The blood pressure was 180 systolic and 85 diastolic, the spinal fluid was normal and sugar was present only in the first specimen of urine. Extensive detachment of the retina followed.

The second patient, a woman aged 41, woke up at night with excruciating headache, numbness of the limbs, visual disturbance and nausea. She had suffered from nervousness and general hypertension for a number of years. Sugar was found in the urine when she was admitted to the hospital, but not later. Large preretinal hemorrhages were present in both eyes, involving the area of disk and macula. Both disks were slightly swollen and the margins indistinct. A cone-shaped livid discoloration at the margin of the disk of the left eye was explained as a result of hemorrhages in the sheath of the optic nerve and in the sclera. Vision returned to normal in the left eye. Some attacks of vascular spasm followed recovery.

The mechanism of preretinal hemorrhages is discussed and their relation to vascular spasm. The hemorrhages are not due to rupture of arteriosclerotic blood vessels, but to arterionecrosis caused by protracted spasmodic contractions.

A third case, that of a woman aged 59, is added. She suffered repeated preretinal hemorrhages alternately in the two eyes in the absence of any etiologic explanation.

K. L. Stoll.

Metastatic Retinitis: Report of Cases. E. Hesse, Klin. Monatsbl. f. Augenh. **105:** 601 (Nov.) 1940.

Hesse discusses the types of metastatic ophthalmia, the benign type described by Axenfeld and the severe septic form described by Roth. He reports on 2 cases of the latter type. Both cases differ from those previously published by the formation of an exudation in the retina, which in the second case assumed the appearance of a hypopyon. Vision

was recovered in both cases, although the symptoms were severe and massive exudations existed. The course of the disease is illustrated by a series of photographs of the fundus in each case. The metastases existed between retina and vitreous, a location more favorable than the parenchyma of the retina. The fibrinous exudation and precipitates in the retina were absorbed. Both patients had a history of tuberculosis, and the second, a man aged 48, presented metastatic inflammation of the tonsils.

K. L. STOLL.

Trachoma

TRACHOMA AND THE WEIL-FELIX REACTION. F. NAGY, Klin. Monatsbl. f. Augenh. **105:** 261 (Sept.) 1940.

Nagy discusses the serologic test of Cuénod and Natax, which opened new roads in research on the causation of trachoma. The role of the rickettsias has not been cleared up, and the theory that lice are transmitters of trachoma has not been accepted. Nagy examined 100 samples of blood serum from patients with severe trachoma who lived in areas in which typhus was not endemic in an attempt to compare his results with those of authors working with persons infested with exanthematous typhus. He used as an antigen Proteus X19 serum, a 1 : 3,200 dilution of which gave positive results in patients with exanthematous typhus. His method is described in detail. Nagy found such a small difference in the Weil-Felix reaction between healthy persons and patients with trachoma that he thinks the reaction is of no consequence for research on the origin of trachoma or for differential diagnosis. No corneal complications existed in his 2 patients with positive reactions, whereas Derkac found positive reactions chiefly in patients with vascularization of the cornea. No connection was discovered between the Weil-Felix reaction and the presence of inclusion bodies.

K. L. STOLL.

Sympathetic Ophthalmia

SYMPATHETIC OPHTHALMITIS. T. H. BUTLER, Brit. J. Ophth. **26:** 546 (Dec.) 1942.

Butler states that during the past ten years he has not had patients with sympathetic ophthalmitis, although during this period he has been most conservative in the treatment of eyes that have suffered from accidents or have given anxiety after operation. Nothing is known about the ultimate cause of the disease. Sympathetic ophthalmitis does not exist apart from a punctured globe. If an eye has been wounded so severely that it has lost its value as an organ of sight, it ought to be removed. Blood counts are of no value in prophylaxis. Neoarsphenamine is regarded as a specific remedy for sympathetic ophthalmitis.

W. ZENTMAYER.

Society Transactions

EDITED BY DR. W. L. BENEDICT

AMERICAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

LAWRENCE T. POST, M.D., *Chairman*

DERRICK VAIL, M.D., *Secretary*

Ninety-Third Annual Session, Atlantic City, N. J., June 10-12, 1942

Lifelong Care of the Eyes. Chairman's Address. DR. LAWRENCE T. POST, St. Louis.

This article was published in full in the July 18, 1942 issue of *The Journal of the American Medical Association.*

Effects Other than Anti-Infectious of Sulfonamide Compounds on Eye. DR. MOACYR E. ALVARO, São Paulo, Brazil

This article was published in full in the April issue of the ARCHIVES, page 615.

Symposium on Geriatrics—Urologic Geriatrics. DR. JOHN H. MORRISSEY, New York.

Among conditions frequent in elderly men are changes of the structures in and about the neck of the bladder. A fair proportion of these are malignant changes. These seem to be accompanied rarely by associated changes in the eye and its adnexa. There is a sufficient proportion of patients in whom ocular disease is present, either in association or as a complication, so that both the ophthalmologist and the urologist should bear in mind the possibility of one condition complicating the other and be familiar with the initial symptoms. The incidence of these complications in different clinics and the end results are discussed. Recent changes in the operative procedures on the prostate, both for benign and for malignant types of obstruction, are less debilitating to the patient. These are discussed from the point of view of the lessened incidence of ophthalmologic complications. Endocrine therapy of certain types of senile atrophic changes in the female genitalia is discussed, with a report of results.

Medical Considerations of Some Geriatric Problems (Lantern Demonstration). DR. GEORGE MORRIS PIERSOL, Philadelphia.

This article was published in full in the January issue of the ARCHIVES, page 26.

Neuropsychiatric Geriatrics (Lantern Demonstration). Dr. Henry W. Woltman, Rochester, Minn.

This article was published in full in the November 1942 issue of the Archives, page 791.

Aging Process in Eye and Adnexa (Lantern Demonstration). Dr. Conrad Berens, New York.

This article was published in full in the February issue of the Archives, page 171.

Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants (Lantern and Motion Pictures Demonstration). Dr. T. L. Terry, Boston.

This article was published in full, with discussion, in the January issue of the Archives, page 36.

Nature, Scope and Significance of Aniseikonia (Lantern Demonstration). Dr. Walter B. Lancaster, Hanover, N. H.

This article was published in full, with discussion, in the November 1942 issue of the Archives, page 767.

Simple Quantitative Test for Acuity and Reliability of Binocular Stereopsis (Lantern Demonstration). Dr. F. H. Verhoeff, Boston.

This article was published in full, with discussion, in the December 1942 issue of the Archives, page 1000.

Dynamics of Intracapsular Cataract Extraction: Experimental Studies with Reference to the Suspensory Ligament and Hannover's Canal and Petit's Space (Lantern Demonstration and Motion Pictures). Dr. Jacob Goldsmith, New York.

This article was published in full, with discussion, in the March issue of the Archives, page 380.

Color Discrimination in Industry (Lantern Demonstration). Joseph Tiffin, Ph.D., Lafayette, Ind., and Dr. Hedwig S. Kuhn, Hammond, Ind.

This article was published in full, with discussion, in the November 1942 issue of the Archives, page 851.

The Removal of Metallic Foreign Bodies from the Eyeball and from the Orbit (Lantern Demonstration). Dr. Edmund B. Spaeth, Philadelphia.

This article was published in full, with discussion, in the Oct. 31, 1942 issue of *The Journal of the American Medical Association,* page 659.

The Ophthalmologist's Place in the Prevention of Traffic Accidents. Dr. Lowell S. Selling, Detroit.

This article was published in full, with discussion, in the Sept. 26, 1942 issue of *The Journal of the American Medical Association,* page 261.

Lymphomatous Tumors of Eye and Its Adnexa (Lantern Demonstration). Dr. John S. McGavic, New York.

This article will be published in full in a later issue of the Archives.

Ocular Changes in Young Diabetic Patients (Lantern Demonstration). Dr. Cecil S. O'Brien and Dr. J. H. Allen, Iowa City.

This article was published in full, with discussion, in the Sept. 19, 1942 issue of *The Journal of the American Medical Association,* page 190.

Ochronosis of the Sclera and Cornea Complicating Alkaptonuria: Review of the Literature and Report of Four Cases (Lantern Demonstration). Dr. James W. Smith, New York.

This article was published in full, with discussion, in the Dec. 19, 1942 issue of *The Journal of the American Medical Association,* page 1282.

DETROIT OPHTHALMOLOGICAL SOCIETY

Howell Begle, M.D., *President*

Edmond L. Cooper, M.D., *Recorder*

Nov. 19, 1942

Pitfalls in Ophthalmic Surgery. Dr. Lawrence T. Post, St. Louis.

Complications are bound to occur in ophthalmic operations, but the incidence can be greatly reduced by proper preparation of both the surgeon and the patient. Adequate anesthesia is important. I have always used a subconjunctival injection of 1 per cent cocaine hydrochloride dissolved in 1:1,000 epinephrine hydrochloride solution just prior to intraocular operations. This renders insensitive the terminal branches of the anterior ciliary nerves and will prevent sudden movement due to pain on the part of the patient. Injection of 1 to 2 cc. of 2 per cent procaine hydrochloride solution retrobulbarly in the region of the ciliary ganglion is performed prior to all intracapsular cataract extractions. Full local anesthesia induced before the removal of sutures will prevent squeezing of the lids and other reactions to pain, which may result in hemorrhage from the iris into the anterior chamber. I have found pentothal sodium a valuable anesthetic for some patients, since it

permits intraocular operations to be done safely on patients who, owing to worry or anxiety, are not good operative risks if operated on under local anesthesia. There is some danger, especially of anoxemia, connected with its use, however, and it should be administered only by a competent anesthetist.

Postoperative prolapse of the iris or the vitreous can be prevented in most cases by the use of corneoscleral sutures. Recently I have found the McLean suture to be very satisfactory. It provides almost an air-tight closure of the wound and does not tend to cause postoperative astigmatism due to corneal irregularity. When a large prolapse of the iris does occur it is treated by excision of the prolapsed tissues and covering of the wound with a conjunctival flap. When the prolapse is small the daily application of concentrated trichloroacetic acid to the prolapse is often satisfactory.

Postoperative infections are best combated before surgical intervention is attempted. All foci of infection should be removed. I advocate thorough treatment of young syphilitic patients prior to operation, but I feel that old patients who have a positive serologic reaction but no other evidence of syphilis may be safely operated on without treatment.

Every one in the operating room should be free from colds and other infections. The patient's face should be free of acne or other infective dermatitis.

HOWELL BEGLE, M.D., *President*

EDMOND L. COOPER, M.D., *Recorder*

Dec. 2, 1942

Physiology and Anatomy of the Extraocular Muscles. DR. HAROLD F. FALLS, Ann Arbor, Mich.

The individual actions of the extraocular muscles in the primary position were reviewed. It was pointed out that with the exception of the external, the rectus muscles are adductors. The superior and inferior oblique muscles are abductors. The action of the superior and inferior rectus muscles and the superior and inferior oblique muscles when the eye is in adduction or abduction was discussed.

It was recalled that the purpose of ocular movements is to extend the field of vision and that the fusion faculty exerts a supreme control over these movements.

The surface anatomy of the eyeball was reviewed, especial emphasis being placed on the distance from the limbus, in millimeters, of the insertions of the tendons of the four rectus muscles, as well as on the length of the tendons themselves. It was pointed out, in this regard, that recession of a muscle is limited by the distance between the original insertion and the equator of the eyeball, while resection of a tendon is limited by the length of the tendon.

Diagnosis of Concomitant Strabismus. Dr. John G. Beall, Ann Arbor, Mich.

Concomitant strabismus is characterized by the fact that the two eyes are equally involved in a muscular imbalance without loss of function on the part of any single muscle. Several facts help differentiate this type of squint from paralytic squint. In concomitant squint the angle of deviation is the same in any direction of gaze and the primary and secondary deviations are the same. There is no limitation of ocular movement in concomitant squint except when the condition is of long standing, when organic shortening of a muscle may occur, resulting in limitation of movement.

Concomitant strabismus may be either alternating or monocular. Alternating convergent strabismus is usually due to absence or extreme weakness of the fusion faculty. Alternating divergent strabismus is due usually to weakness of the fusion faculty or to weakness of accommodation. Monocular strabismus is more often due to refractive errors (more commonly hypermetropia), especially a difference in refractive error in the two eyes (anisometropia).

Proper treatment of concomitant squint is dependent on accurate diagnosis. Careful study of each case of strabismus should include (1) history, including age of the patient at onset, and constancy of the squint; (2) heredity; (3) central vision with and without correcting lenses; (4) fixation; (5) measurement of the angle kappa; (6) character of the squint; (7) measurement of the angle of deviation with and without correcting lenses; (8) refractive error, and (9) fusion faculty.

Surgical Treatment of Strabismus. Dr. F. B. Fralick, Ann Arbor, Mich.

A consideration of the surgical treatment of strabismus should deal largely with the determination and evaluation of the preoperative findings. Surgical intervention should not be considered until the following data are available: (1) the refractive error determined during atropine cycloplegia; (2) the visual acuity with the correction determined during cycloplegia; (3) the presence or absence of the fusion faculty and its degree; (4) the presence or absence of diplopia; (5) the deviation, with and without cycloplegic correction, at 6 meters and 33 cm. and in the six cardinal directions of gaze; (6) the near point of convergence, and (7) the ocular movements in the six cardinal directions of gaze in the cover test.

If the accommodative element is absent when tested by measurement of the angle of squint with and without glasses, glasses should not be prescribed for the squint alone, since the angle of squint will not be lessened by the glasses. The purely accommodative type of squint does not require surgical correction, but the patient should be referred to an orthoptic technician, if available, so that an attempt may be made to break up the convergence-accommodation association. When the squint is partly accommodative and partly mechanical, the mechanical portion should be corrected surgically, largely by a strengthening operation on the external rectus muscle, supplemented when necessary by a central tenotomy or a minimal recession of the internal rectus muscle. Every effort should be made to conserve the power of convergence.

As far as possible, one should determine whether the squint is a convergence anomaly (excess or insufficiency) according to Duane's classification, a divergence anomaly (excess or insufficiency) or a combination of the two. There will then be little doubt as to whether a strengthening operation (resection, cinch, etc.) or a weakening operation (recession, guarded tenotomy, etc.) is indicated. The selection of the external muscle or the internal muscle to be operated on may be influenced by the screen test with the eyes in the six cardinal directions of gaze. By this study a paretic muscle may be uncovered.

Brown and White have demonstrated the poor results obtained by the use of glasses, orthoptic training and surgical intervention in the treatment of convergent strabismus complicated by a vertical imbalance unless the vertical anomaly is corrected. Generally, the vertical deviation should be corrected first, but in the higher degrees of lateral deviation it is often necessary to correct a part of the horizontal deviation in order to study the vertical deviation accurately. In such cases the surgical correction should be confined to the external muscle.

In esotropia, the surgical correction should be such that a near point of convergence of around 90 mm. is maintained or developed. A weakening of the internal muscle is more necessary in cases in which there is spasmodic in-shooting than in other cases. In cases of esotropia in which the near point is 90 mm. or over, the surgical correction should be accomplished primarily by shortening the external muscle, and in cases of exotropia, it should be accomplished by shortening the internal muscle.

The optimum time for operation is when no progress in reduction of the squint is being achieved with nonoperative measures. The earlier the nonsurgical measures are carried out, the more likely that one will be able to obtain a functional result by surgical correction if it is needed.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

DANIEL B. KIRBY, *Chairman*

R. TOWNLEY PATON, *Secretary*

Dec. 21, 1942

Unsuccessful Cataract Extractions. DR. THEODORE L. TERRY (by invitation).

The lesions present after unsuccessful cataract extractions, as revealed chiefly in enucleated eyes, are more or less unrelated and of varied importance. A brief analysis shows that they can be divided into five general groups.

1. Lesions arising through failure to remove the lens or part of the lens, such as the nucleus, capsule or cortex, with proliferation of new abnormal lens fibers.

2. Lesions arising through prolapse or expulsion of materials from the eye, including practically all the normal intraocular structures, and hemorrhage.

3. Lesions arising through introduction of material foreign to the interior of the eye, namely, micro-organisms; particulate matter, such as talc (when rubber gloves are worn the hands are usually first dusted with talc powder, much or most of which escapes into the air of the operating room); drugs, such as the sulfonamide compounds; ointment; stitches, and even surface epithelium.

4. Lesions arising through stimulation of degenerative or productive changes resulting directly or indirectly from the operation, such as exacerbation of corneal dystrophy; rapid spread of pterygium; fibrosis or atrophy of the iris, frequently associated with pigment scattered widespread throughout the eye as a result of proliferation of the pigment epithelium of the iris; mechanical blockage of the iris angle; fibrosis of cyclitic membrane; retardation of the "secretory" function of the ciliary body; changes in the hyaloid membrane necessitating discission even after intracapsular extraction; fluid formation or opacification of the vitreous, and separation of the retina and, more rarely, of unpigmented ciliary epithelium.

5. Intraocular neoplasm hidden by the cataract.

DISCUSSION

DR. JOHN M. MCLEAN, Baltimore: Dr. Terry's interesting paper is so complete in itself that there is little or no room for discussion from the pathologic point of view, but he has brought up several subjects that I think are worth further discussion from the clinical aspect. One of his points was the question of corneoscleral sutures. I stated before this section three years ago that there were three ways of closing cataract wounds: (1) with no sutures, (2) with conjunctival sutures and (3) with corneoscleral sutures. I should now like to amend that statement to say that I think there are four ways: (1) without sutures (a non-surgical procedure which is fortunately obsolete); (2) with conjunctival sutures, which are gradually being replaced by corneoscleral sutures; (3) with corneoscleral sutures that are adequate to close the wound properly, and (4) with sutures that are labeled corneoscleral sutures but cause a great deal of unfavorable comment (i. e., long surface sutures, which allow the wound to become displaced laterally; sutures which are not really in the cornea or sclera at all, and sutures which disturb the closure of the wound and cause imperfect approximation). I believe it cannot be disputed that corneoscleral sutures do have great advantages. When they are properly placed they lessen the incidence of astigmatism and postoperative hemorrhage, and I think most of the criticism concerning them comes from persons who do not use them properly. They also reduce the incidence of postoperative prolapse of the iris. There is little need to worry about a patient's getting out of bed shortly after operation if suitable corneoscleral sutures have been used; I prefer to have an elderly patient get out of bed to void rather than to have him catheterized. A corneoscleral suture should be inserted in solid corneal tissue and not in loose, yielding conjunctival tissue. It should be placed before the section is made and should not require extensive manipulations after the eye is closed. It should go through,

not over, the lips of the wound, so as to give firm closure without danger of inversion of the edges, and it should be so placed that when tied it will bring the tissues back to exactly the preoperative position. The Verhoeff rethreaded suture meets these requirements, and I used it until I found what I think is a better suture. I have only two objections to the type of suture mentioned by Dr. Terry: The first is a practical one, pertaining to the time interval after the eye is opened before suture control is available. Rethreading the suture needle is not difficult, provided the patient cooperates, but if one has an unruly patient or a serious complication after incision and must thread the suture needle, serious trouble may ensue. The other objection is theoretic and involves the closure of the epithelium in such a way that the possibility of epithelial ingrowth is increased. The latter objection may or may not be supported by the fact that Dr. Terry has recently found a greater incidence of epithelial ingrowth in Boston.

An old type of corneoscleral suture of which the principle is widely used is the original Kalt suture. If it is tied too tightly or if pressure occurs within the eye postoperatively, the lips of the wound have a tendency to become inverted, with resultant rupture of the small blood vessels and hemorrhage into the anterior chamber. Of course if the suture is tied too loosely it might as well be a conjunctival suture in the first place.

Another subject which Dr. Terry mentioned was the old, old question of intracapsular extraction versus extracapsular extraction. I have been told I am very radical. I feel there is one definite indication for extracapsular extraction, and that is some mechanical obstruction, such as extensive posterior synechias, which make it impossible to get the lens out in the capsule. It has been said that the presence of myopia or of fluid vitreous, or youth, is a contraindication to intracapsular extraction. I do not agree, and I have done intracapsular extractions under all these circumstances. This operation can be done satisfactorily on young persons; it is not necessary to wait until the patient is 65 or any other arbitrary age. I see no reason why myopia or fluid vitreous should be an objection. Vitreous will not run uphill. It has to be pushed uphill, and if it is not pushed uphill the risk of losing it is not any greater than in an extracapsular operation. There is much more to be said on this subject, but I think perhaps a few of the other points in Dr. Terry's paper should be discussed.

Dr. Terry mentioned talc powder becoming lodged in the eye from the use of rubber gloves. That is a result of bad technic. I don't see any reason why gloves should not be used. Slowly but steadily all modern ophthalmic institutions are adopting their use in all operations on the eyes.

Finally, Dr. Terry spoke of introducing foreign material into the eye, including bacteria. One of the sources of the introduction of bacteria is contamination from bottles containing solutions that are instilled into the eye at the end of an operation or during postoperative dressings. For this reason there has been put into effect at the Johns Hopkins Hospital a system whereby small dropper bottles are made up and an individual one provided for each patient. These bottles are filled in the pharmacy, and the alkaloid materials which are harmed by sterilization with heat do not need to go through the autoclave. The filled

bottles can be sterilized by the pharmacist according to the Seitz filtration method and can be handled in the operating room just as one might handle suture ampules. One little bottle will serve for a patient and can then be discarded. I thought this system would turn out to be wasteful and expensive, but the chief pharmacist at the hospital insists that the saving, particularly the saving of the alkaloid drugs used, is no less than 85 per cent.

DR. ARNOLD KNAPP: I think that to persons who are working in the operating room there is nothing more important than to have a visual recollection of the pathologist's teachings about what goes on during an operation and afterward. One of the most important articles I have read was "The Pathologist in the Operating Room," by Treacher Collins.

Dr. Terry has brought out some important points in his paper. I should like to limit my remarks to three matters.

The first is, What happens to the nucleus? I remember a case of traumatic cataract in an elderly man (I think there was only the one eye) in which the nucleus escaped into the vitreous through a posterior opening in the capsule and could not be gotten out. The nucleus was let alone and the patient followed for many months, and fortunately the nucleus ultimately worked its way into the anterior chamber, from which it was possible to extract it.

The second point concerns endothelial dystrophy. I have had some cases in which operation has not made this unfortunate complication worse; I have never seen it get better. I do not mean by endothelial dystrophy the opacities of the cornea which arise if the cataract is forced through too small an incision.

Finally, I should like more information on the ingrowth of epithelium into the anterior chamber. I never heard before that this has been observed after a discission operation. I should like to have Dr. Terry amplify his remarks on the development of such epithelization and also tell what results he has obtained by using roentgen ray therapy for it.

DR. THEODORE L. TERRY: The agreement between Dr. McLean and myself is indeed complete. Corneoscleral stitches appear to do away with expulsive hemorrhages that would ordinarily occur after the patient left the operating room. In one instance a rather large hemorrhage did occur, and, although there was some bulging at one corner of the section, the stitches held. The hemorrhage largely subsided, and the patient eventually obtained 20/200 vision. Without efficient suturing the anterior chamber is apt to break down several times before it is permanently formed, and expulsive hemorrhages can occur whenever the chamber is lost.

Relative to the age at which intracapsular extraction can be done, I was once surprised to find that I had dislocated an abnormally large congenital cataract in a girl 16 years of age when I grasped the capsule with toothed forceps to remove a large portion of it as a part of a linear cataract extraction. By widening the keratome incision it was possible to remove the lens within its capsule. This girl was anxious to obtain a black pupil before she attended a national young people's

meeting as a delegate. I have since seen the same thing happen when another surgeon was operating, but I do not recommend the procedure as a routine.

Extraction of the lens in the presence of high myopia has also been successful. At the Massachusetts Eye and Ear Infirmary, I saw the late results of a series of such operations performed by Dr. E. B. Dunphy. The results were as impressive to me as they were pleasing to the patients.

The only possible disagreement that I might have with Dr. McLean might arise through the approach to more satisfactory asepsis through the use of gloves and individual ampules of alkaloid medications. I wonder whether enough attention is paid to asepsis. This question arose after I had heard an exhaustive communication by a staff member of the Peter Bent Brigham Hospital concerning the sterilization of operating room goods. It was shown that there is a tendency to develop superheated steam, which, owing to its dryness, does not sterilize for a number of hours and in turn causes a charring of the wrapping. The spore bearers, molds and yeast are the micro-organisms most apt to survive. Also, the impatience of the surgeon who is awaiting his instruments magnifies the time they are in the sterilizer, so that in response to his demand for his instruments they are given to him before complete sterilization has taken place.

Dr. Knapp's remarks are, as usual, very interesting. It is well to know that corneal dystrophies are not invariably made worse by operations for cataract. His graphic remarks concerning the effect on the cornea of too small incisions are important.

Concerning epithelial ingrowth, the case which he questions was published in the *American Journal of Ophthalmology* (**22**: 1087 [Oct.] 1939); it was case 12. An epithelial cyst was removed from the eye two years after two incisions had been made by Dr. George Derby. The history obtained from unusually intelligent parents was convincing that there had been no perforations of the eye other than the two discissions. This instance caused me to investigate the possibility of irregularities on ophthalmic cutting instruments. Under the microscope numerous irregularities of sufficient size to carry in several epithelial cells were observed. Perhaps epithelization can result from the planting in fertile ground of a single cell from the basal layer of the epithelium. This possibility is borne out by the success of epithelial transplantation by means of hypodermic injection of emulsified epithelial scrapings into the superficial portion of granulation tissue. Relative to treatment of epithelial ingrowth, I am sorry to have to report that the results obtained were not comparable to those reported by Dr. Derrick Vail for irradiation. In fact, I have seen no patient benefited by this treatment and the roentgenologist at the Massachusetts General Hospital refuses to treat any more patients, since he is convinced that normal adult epithelium within the eye cannot be destroyed without irreparable damage to the eye itself.

Hearing Dr. Knapp's discussion reminds me that I failed to present an important point concerning the ultimate results of brutal massage to the ciliary body during an operation. I have heard Dr. Knapp say that his father had observed that such massage leads to bad results through an abnormally low tension.

Catgut Sutures in Cataract Extractions. DR. WENDELL L. HUGHES.

After experimentation with various types of suture material, including nylon, plastic and various sizes of plain and chromic catgut, a special suture material of plain catgut was made up by Davis and Geck (P322). After an experimental period of almost a year in which one silk and one catgut suture were used in each eye, it was found that the plain catgut suture caused the same or possibly slightly more corneal reaction, while the conjunctival and the general reaction of the eye was about the same whether silk or catgut had been used. A modified Stallard suture had been used in all cases. The catgut suture material was more rigid than the silk even after soaking for five minutes in 5 per cent glycerin and saline solution.

This suture material was spontaneously absorbed in five to eight days. The advantage of spontaneous absorbability is, of course, self evident, in that no complications from removal of the sutures can endanger the ultimate result. These complications consist particularly of (1) hemorrhage, (2) springing of the wound and (3) loss of the anterior chamber.

It was felt that this was not the ideal suture material but that it was a step toward realization of the ideal for cataract extractions. It was felt that especially in emergency war operations the employment of catgut sutures might be important, as it would not always be possible to determine who would be present to remove silk sutures.

DISCUSSION

DR. LOREN P. GUY: Since the beginning of aseptic surgery, and probably before, there has been a search for better and still better suture material. This quest has been both for a general all around material and for special substances for particular work, such as repair of hernia and operations on the brain. Now Dr. Hughes has sought to find a satisfactory absorbable suture material for cataract extractions. Obtaining this objective is obviously desirable. All ophthalmic surgeons know what a hazard it is to remove sutures after an intraocular operation.

Since the days of William Stewart Halsted (Ligature and Suture Material, *J. A. M. A.* **60:** 1119 [April 12] 1913) silk has been considered the best and the safest suture material. Dr. Halsted's objections to the use of catgut have ever remained a challenge.

First of the arguments of Dr. Halsted was the greater cost of catgut over silk. This may be a great factor in general surgical procedures, in which so many sutures are needed. In operations for cataract only one or two sutures are needed; the cost is consequently less and hardly a factor.

Catgut thread is bulky, but no. 00000 soaked in 5 per cent glycerin and saline solution is handled easily enough, although not as easily as silk. In no instance did bulkiness and inconvenience of use complicate the operation. It might have been better had the sutures been colored so that they could more easily be identified. The matter of color, however, is being considered.

The history of the use of catgut sutures has been darkened too often by disasters due to faulty sterilization. In New York in 1927, in one of the best run hospitals, 5 deaths from gas gangrene (Meleney, F. L.;

Humphreys, F. B., and Carp, L.: Unusual Fatal Operative Wound Infection Yielding Pathogenic Anaerobe of Gas Gangrene Group Not Hitherto Described, with Direct Reference to Catgut as Source, *Surg., Gynec. & Obst.* **45:** 775, 1927) were caused by septic catgut sutures. In 1940 Dr. Frank L. Meleney (Problem of Catgut Sterility, *Internat. Abstr. Surg.* **71:** 422, 1940; in *Surg., Gynec. & Obst.,* November 1940) reported that of one hundred and seventy-four specimens of catgut purchased on the open market twenty-two were contaminated. Fortunately there was no infection in this study on human patients. In experiments on rabbits, Dr. Romaine reported infections which most likely did not come from the suture material. Any one who has operated on rabbit eyes knows how difficult it is to prevent infection. However, infection is still a factor to be considered. The recent Food, Drug and Cosmetic Act covers suture material, and for the first time there is financial as well as legal power to prevent faulty and contaminated suture material from being sold. Yet one must be ever alert and aware.

Dr. Halsted considered catgut inadequate and distrusted its absorbability. If one considers four or five days long enough for a suture to hold after an operation for cataract, then the suture material Dr. Hughes has described is adequate. In the cases I observed, it was uniformly absorbed within a day or two; there was no uncertainty.

Dr. Romaine demonstrated histologically in his work on rabbits that there was more reaction to plain catgut than to silk. This was not apparent clinically in human beings. There was only a mild reaction to the plain catgut, and the reaction was little if any greater than to silk.

The suture material described answers as adequately as has ever been answered the classic challenges of Dr. Halsted. In addition, it is absorbable, and it is an obvious blessing to the surgeon and to the patient to eliminate the discomfort and risk of removing sutures.

Spontaneous Cysts of Iris: Report of a Case. DR. HERBERT KATZIN (by invitation).

Spontaneous cysts of the iris are either of congenital type, formed between the layers of the pigment epithelium, or developmental, occurring in the stroma. The former type results from incomplete closure of the annular sinus, which is the most anterior extremity of the primitive optic vesicle. These cysts are often multiple, are familial and usually occur at the pupillary margin. They may be nonprogressive. The developmental cysts arise by cystoid change in endothelial or epithelial cell rests which invade the iris during fetal life. Some may arise by serous enlargement of cavities in the iris bridged over by endothelium. The cyst wall may have single cell or multiple cell layers. The cells may be cuboid, columnar or even goblet types. The epithelium may originate in the surface ectoderm or the anterior pigment layer or may even migrate secondarily from lens vesicle epithelium.

The natural course of the disorder consists of a symptom-free period followed by recurrent iridocyclitis, intractable glaucoma and blindness.

The differential diagnosis between a cyst, a tumor and an inflammatory mass is aided by the presence of a transparent wall, mobility, multiplicity, a notched margin or tremulousness. Iridectomy or puncture may be helpful on occasion.

The treatment of choice is excision by iridectomy.

I should like to report the case of a 21 year old girl who had no complaints. She noticed the lesion herself. The cyst in the left eye, extended from 1 : 30 to 4 : 30 o'clock, from within the angle to a distance 1 mm. from the pupillary margin. The anterior wall was translucent and contained a few pigment flecks. It encroached on the cornea, rendering its posterior surface opaque for 2 mm. The cyst increased in size during three months' observation; so excision was performed. It was found to lie within the stroma and to be lined with ectodermal epithelium of varying thickness. A few inflammatory cells were present. The postoperative result was excellent except for the development of moderate astigmatism.

DISCUSSION

DR. KAUFMAN SCHLIVEK: Spontaneous cysts of the iris are rare. There is strong evidence to show that they are developmental. In 1935, F. Blobner found only 49 cases reported in the literature. Of 45 patients, 6 were under 1 year of age, 3 under 2, 11 between 3 and 10, 8 between 11 and 20 and 17 over 20. The oldest patient was 69.

While occasionally such a cyst may not be troublesome, when it begins to grow something must be done. If the cyst is not destroyed or removed, vision will be lost, glaucoma will ensue and enucleation may be necessary. The best treatment consists of iridectomy with complete excision of the cyst. Several authors have recommended this procedure (Moore, R. F.: Two Cases of Epithelial Implantation Cyst of Iris, *Brit. J. Ophth.* **14:** 496, 1930. Villard, H., and Dejean, C.: Les kystes de l'iris, *Arch. d'opht.* **50:** 91, 194 and 272, 1933. Blobner, F.: Spontane Irisstromazyste, *Klin. Monatsbl. f. Augenh.* **95:** 478, 1935).

If complete removal is not feasible other procedures may be used. The following are mentioned in the literature: (1) injection of sclerosing solutions (Duke-Elder. Wright, R. E.: Cyst of Iris, *Brit. J. Ophth.* **54:** 423, 1925); (2) puncture (Treacher Collins); (3) partial excision of the cyst wall and prolapse of the iris under the conjunctiva (Christie Reid); (4) electrocoagulation (Šafář, K.: Ueber eine Iriszyste im aphaken Auge, durch Elektrokoagulation geheilt, *Ztschr. f. Augenh.* **86:** 31, 1935); (5) radiotherapy (Vail, D.: Epithelial Downgrowth into Anterior Chamber Following Cataract Extraction: Arrest by Radium Treatment, ARCH. OPHTH. **15:** 270 [Feb.] 1936. Perera, C. A.: Epithelium in Anterior Chamber of Eye After Operation and Injury, *Am. J. Ophth.* **21:** 605, 1938), and electrolysis (Bourdier, F., and Stein: Kyste traumatique de l'iris, *Bull. Soc. d'opht. de Paris* **49:** 731, 1937. Villard and Dejean).

I have seen only one patient besides the one reported on by Dr. Katzin, and that was in 1928. Dr. de Schweinitz saw the patient, a girl 18 months old, in consultation, and he said that he had had no experience with the treatment of congenital cysts of the iris. Dr. Arnold Knapp also saw the child, and he stated that he had never seen a congenital cyst of the iris. The pediatrician who referred the patient had made a diagnosis of conjunctivitis. The eye had been red for three and a half weeks when I first saw her, on July 13, 1928. Examination revealed evidence of fibrinous iritis. Posterior synechias were present. In the lower temporal quadrant an oval gray cyst in the iris was discernible. It was about 4 mm. high by 3 mm. wide and invaded the

pupillary area. The periphery of the iris was not involved. The iritis responded to use of atropine sulfate and hot compresses. On September 4 the cyst had grown. The mass transmitted light. Because of the rapid growth, excision was advised. Dr. Knapp felt that Wright's recommendation to inject phenol after the cyst had been removed was a good one, but he preferred the use of iodine. The cyst was aspirated, and Dr. Knapp injected a few drops of a 3 per cent solution of iodine. The reaction continued for a few weeks.

Recently Dr. Knapp sent me a report of the progress of the case. Four months after the operation the cyst was definitely smaller. There was an opacity in the lower half of the cornea. Three months later the cyst had shrunk to a very small mass. The cornea was clear. The following month there was no evidence of cyst. The iris was adherent to the posterior corneal surface at the point where the cyst had been present. This condition has persisted, and when the patient was last seen, in October 1942, the vision in the right eye was 5/200. There was a circumscribed opacity of the cornea, and the iris was adherent down and out. The tension was normal.

In the case reported by Dr. Katzin, operation was advised as soon as the cyst increased in size. The keratome was inserted 2 mm. outside the limbus above the cystic mass. With Stevens' scissors the wound was enlarged until the lower margin of the cyst was reached. The iris was grasped at the sphincter, and without difficulty the cyst was everted. With one cut of de Wecker scissors the whole cyst, with little normal tissue, was excised; sutures were inserted.

DR. THEODORE L. TERRY: Dr. Katzin is to be congratulated on the success of the surgical removal of the cyst.

This brings to mind the question of what should be done if the cyst cannot be removed. Dr. Jonas Friedenwald pointed out the destruction of bile on corneal epithelium. It would be interesting if some one would determine whether or not an eye which could not be operated on would tolerate bile injected into and aspirated from a cyst as a measure that might effectively destroy the epithelial lining.

Tuberous Sclerosis: Report of a Case. DR. ELIZABETH F. CONSTANTINE.

This paper will be published in full, with discussion, in a later issue of the ARCHIVES.

The following abstract of a paper presented at the Nov. 16, 1942 meeting and the discussion were omitted from the report published in the March issue of the ARCHIVES (page 518):

Neurodermatitis with Cataract. DR. CLYDE E. MCDANNALD.

A study of 2 cases of neurodermatitis with cataract, together with a historical survey of the disease and a thorough consideration of etiology, led to the following conclusion: The patients were emotionally unstable and reacted to many allergic tests. The skin of the lids was brawny, red and itchy, with no involvement of the cilia, as reported by some observers. In 1 case the conjunctiva was slightly inflamed. The cataractous lenses were soft and easily removed by irrigation; neither patient showed definite evidence of a nucleus. Both patients were young and in an active stage of eczema and neurodermatitis. Neither of them

showed undue postoperative reaction. Both were of the white race. The cataracts matured rapidly (about one and a half years). Most likely many cases of this combination of conditions are overlooked and reported merely as instances of congenital cataract. The occurrence of conical cornea was possibly coincidental. Cataracts like these lend themselves especially well to surgical treatment and seem to be no more hazardous than other types of cataracts.

DISCUSSION

DR. TRUMAN L. BOYES: I wish first to present the following case:

A 24 year old white woman first consulted me on Aug. 21, 1935 for routine ocular examination. She had been under treatment for eczema since she was 6 years of age, and recently the dermatologist had changed the diagnosis to neurodermatitis. The father was well and the mother inclined to be somewhat emotionally unstable. The patient was an only child. On the maternal side, three first cousins had asthma and allergy and one moderate neurodermatitis. The patient's birth was normal, and she was apparently well until she was 6, when her parents first observed a cutaneous eruption, which was diagnosed as eczema. The menstrual cycle was normal. She was married at the age of 19 and had one child living and well.

On August 21 the vision in each eye was 20/100, corrected with — 1.50 D. sph. to 20/20. The lids were slightly brawny, the conjunctiva was moderately congested and she complained of itching. The cilia were normal. On Dec. 15, 1936 she stated that for the past year the allergic condition had been more severe in the eyes and now involved the scalp and body. During this period she was under the care of a dermatologist and reported improvement with the use of mixed vitamins and a vaccine made of virus from skin. The skin of the lids was brawny and very itchy. The corrected vision in each eye was 20/20 +.

On Nov. 5, 1938, approximately three years from the time of my original examination, she stated that the vision in the left eye had been failing for one month. The corrected vision was 20/20 in the right eye and 20/200 in the left. The reduced vision in the left eye was due to a complicated cataract. The changes were shallow in the cortex just beneath the capsule anteriorly and posteriorly, with discrete grayish white dots, in places becoming confluent. Only a red fundus reflex was seen. After the patient had spent several months in Florida the condition of the skin had shown some improvement.

On Aug. 5, 1939 the right lens was clear and vision in the right eye was normal with correction. Vision in the left eye was 20/533. The left lens was cataractous and grayish white and the cataract mature (maturation took about one year). On July 16, 1940 the vision with correction was 20/20 in the right eye and 20/533 in the left. Subcapsular changes in the cortex were seen for the first time in the right eye. On Jan. 8, 1942 vision with correction was 20/20 in the right eye and perception of hand movement in the left. Subcapsular changes were present in the right lens, mostly on the temporal side. The left lens showed a mature cataract and was white, with no iris reflex. The patient was ready for operation.

On January 14 I performed a linear extraction on the left eye. A keratome section was made, and the small nucleus and all soft lenticular matter were washed out. No iridectomy was done. Pilocarpine nitrate

solution was instilled at the time of operation and a 1 per cent solution of atropine sulfate the following day. On February 13, one month after the patient's dismissal from the hospital, vision in the left eye was 20/20 with the following correction: + 9.00 D. sph. ⊃ + 1.50 D. cyl., axis 30. The date of the last examination was October 2, at which time the vision in the right eye was 20/25 with the following correction: — 0.75 D. sph. ⊃ — 0.25 D. cyl., axis 60. The changes in the right crystalline lens were anterior and posterior cortical and the nucleus clear. The patient is now under the care of a physician, who has helped her greatly with concentrated vitamins and double doses of calcium gluconate administered intravenously three times a day. She is also receiving a preparation containing phenobarbital with small amounts of ergotamine tartrate and belladonna alkaloid (bellergan).

To summarize: 1. The patient was very nervous and emotionally unstable. 2. No change in the cutaneous condition occurred during pregnancy. 3. The cataract matured rapidly (in less than one year). 4. The cataract was situated in the cortex just beneath the capsule, as in most cases of cataract associated with neurodermatitis. 5. The eyes were normal previous to the development of the cataract. This is consistent with the literature.

Several authors have thought such cataracts due to endocrine dysfunction or to the use of ultraviolet rays or roentgen rays, but there is not enough evidence to support this view. Approximately 35 cases have now been reported in the English and European literature.

DR. DANIEL B. KIRBY: I should like to know whether any one can throw light on the causation of the condition and the relation between the neurologic or dermatologic condition and the formation of the cataract.

DR. ARNOLD KNAPP: Dr. Kirby has drawn attention to the real point of the whole question: What type of opacity does one find in the lenses of such patients? Through the courtesy of Dr. McDannald I saw his first patient and found a large posterior cortical cataract and a somewhat smaller anterior cortical cataract. The anterior cortical opacity was not subcapsular; it was definitely in the stroma of the anterior cortex. If one considers the opacities of the lens which develop in the cortex, leaving aside the well known cuneiform and posterior cortical types, one has a group of opacities which includes those of tetany, of myotonic dystrophy and possibly of diabetes, and one must also include the cataract in neurodermatitis.

DR. MORRIS JAFFE: I have under my care a young man who has had bilateral subcapsular cataracts associated with this cutaneous condition. After fifteen months of treatment his skin no longer looked red and leathery or his lids edematous. He was moderately myopic, and originally his vision could be improved to 20/40 in each eye. To my surprise it improved to 20/30 with the improvement of the cutaneous condition. There was no absorption of opacities in the lens, but the condition definitely became stationary.

DR. CLYDE E. MCDANNALD: Patients with neurodermatitis seem to recover spontaneously around the age of 40. The question of heredity is occasionally brought up by a patient contemplating marriage. Dermatologists seem to think there is little danger of transmission of the disease.